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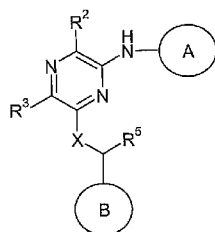
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(54) Title: PYRAZOLYL-AMINO-SUBSTITUTED PYRAZINES AND THEIR USE FOR THE TREATMENT OF CANCER



Formula (I)

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

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**PYRAZOLYL-AMINO-SUBSTITUTED PYRAZINES
AND THEIR USE FOR THE TREATMENT OF CANCER**

Field of the Invention

The present invention relates to a novel compound, its 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 this compound in the manufacture of medicaments for use in the treatment and prevention of myeloproliferative disorders and cancers.

Background of the Invention

Receptor tyrosine kinases (RTK's) are a sub-family of protein kinases that play a critical role in cell signalling and are involved in a variety of cancer related processes including cell proliferation, survival, angiogenesis and metastasis. Currently up to 100 different RTK's including tropomyosin-related kinases (Trk's) have been identified.

Trk's are the high affinity receptors activated by a group of soluble growth factors called neurotrophins (NT). The Trk receptor family has three members - TrkA, TrkB and TrkC. Among the NTs there are (i) nerve growth factor (NGF) which activates TrkA, (ii) brain-derived growth factor (BDNF) and NT-4/5 which activate TrkB and (iii) NT3 which activates TrkC. Each Trk receptor contains an extra-cellular domain (ligand binding), a trans-membrane region and an intra-cellular domain (including kinase domain). Upon binding of the ligand, the kinase catalyzes auto-phosphorylation and triggers downstream signal transduction pathways.

Trk's are widely expressed in neuronal tissue during its development where Trk's are critical for the maintenance and survival of these cells. A post-embryonic role for the Trk/neurotrophin axis (or pathway), however, remains in question. There are reports showing that Trk's play important role in both development and function of the nervous system (Patapoutian, A. et al *Current Opinion in Neurobiology*, 2001, 11, 272-280).

In the past decade, a considerable number of literature documentations linking Trk signalling with cancer have published. For example, while Trk's are expressed at low levels outside the nervous system in the adult, Trk expression is increased in late stage prostate cancers. Both normal prostate tissue and androgen- dependent prostate tumors express low levels of Trk A and

undetectable levels of Trk B and C. However, all isoforms of Trk receptors as well as their cognate ligands are up-regulated in late stage, androgen- independent prostate cancer. There is additional evidence that these late stage prostate cancer cells become dependent on the Trk/neurotrophin axis for their survival. Therefore, Trk inhibitors may yield a class of apoptosis-inducing agents specific for androgen- independent prostate cancer (Weeraratna, A. T. et al *The Prostate*, 2000, 45, I40-I48).

Furthermore, the literature also shows that over-expression, activation, amplification and/or mutation of Trk's are associated with secretory breast carcinoma (*Cancer Cell*, 2002, 2, 367-376), colorectal cancer (Bardelli et al *Science*, 2003, 300, 949-949) and ovarian cancer (Davidson, B. et al *Clinical Cancer Research*, 2003, 9, 2248-2259).

There are a few reports of selective Trk tyrosine kinase inhibitors. Cephalon described CEP-751, CEP-701 (George, D. et al *Cancer Research*, 1999, 59, 2395-2341) and other indolocarbazole analogues (WO0114380) as Trk inhibitors. It was shown that CEP-701 and/or CEP751, when combined with surgically or chemically induced androgen ablation, offered better efficacy compared with mono-therapy alone. GlaxoSmithKline disclosed certain oxindole compounds as Trk A inhibitors in WO0220479 and WO0220513. Recently, Japan Tobacco reported pyrazolyl condensed cyclic compounds as Trk inhibitors (JP2003231687A). Pfizer also recently published certain isothiazole Trk A inhibitors (Bioorg. Med. Chem. Lett. 2006, 16, 3444-3448).

In addition to the above, Vertex Pharmaceuticals have described pyrazole compounds as inhibitors of GSK3, Aurora, etc. in WO0250065, WO0262789, WO03027111 and WO200437814; and AstraZeneca have reported pyrazole compounds as inhibitors against IGF-1 receptor kinase (WO0348133). AstraZeneca have also reported Trk inhibitors in International Applications WO 2005/049033, WO 2005/103010, WO 2006/082392, WO 2006/087530, and WO 2006/087538.

Another such family of RTK's is the JAK family. The JAK (Janus-associated kinase)/STAT (signal transducers and activators or 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-1) 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).

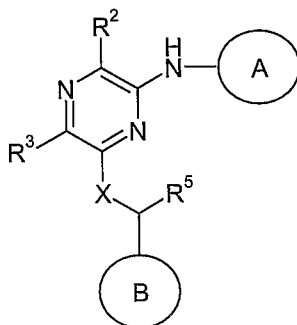
Several mutated forms of JAK2 have been identified in a variety of disease settings. For example, translocations resulting in the fusion of the JAK2 kinase domain with an oligomerization domain, TEL-JAK2, Bcr-JAK2 and PCM1-JAK2, have been implicated in the pathogenesis of various hematologic malignancies (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 thrombocythemia 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 critical role in driving these diseases (MJ Percy and McMullin MF, Hematological Oncology 2005, 23(3-4), 91-93).

JAKs (in particular JAK3) play an important biological roles in the immunosuppressive field and there are reports of using JAK kinase inhibitors as tools to prevent organ transplant rejections (Changelian, P.S. et al, Science, 2003, 302, 875-878). Merck (Thompson, J. E. et al Bioorg. Med. Chem. Lett. 2002, 12, 1219-1223) and Incyte (WO2005/105814) reported imidazole based JAK2/3 inhibitors with enzyme potency at single nM levels. Recent Vertex PCT publications have described azaindoles as JAK inhibitors (WO2005/95400). AstraZeneca has published quinoline-3-carboxamides as JAK3 inhibitors (WO2002/92571).

In addition to the above, Vertex Pharmaceuticals has described pyrazole compounds as inhibitors of GSK3, Aurora, etc. in WO2002/50065, WO2002/62789, WO2003/027111 and WO2004/37814; and AstraZeneca has reported pyrazole compounds as inhibitors against IGF-1 receptor kinase – WO2003/48133 - and Trk in WO2005/049033, WO2005/103010, WO2006/082392.

Summary of the Invention

In accordance with the present invention, the applicants have hereby discovered novel pyrazine compounds of Formula (I):



Formula (I)

or pharmaceutically acceptable salts thereof.

The compounds of Formula (I) are believed to possess Trk kinase inhibitory activity and are accordingly useful for their anti-proliferation and/or proapoptotic (such as anti-cancer) activity and in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said pyrazine compounds, or pharmaceutically acceptable salts thereof, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments for use in the production of an anti-proliferation and/or proapoptotic effect in warm-blooded animals such as man.

Also in accordance with the present invention the applicants provide methods of using such compounds, or pharmaceutically acceptable salts thereof, in the treatment of cancer.

The properties of the compounds of Formula (I) are expected to be of value in the treatment of disease states associated with cell proliferation such as cancers (solid tumors and leukemia), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

Furthermore, the compounds of Formula (I), or pharmaceutically acceptable salts thereof, are expected to be of value in the treatment or prophylaxis of cancers selected from congenital fibrosarcoma, mesoblastic nephroma, mesothelioma, acute myeloblastic leukemia, acute lymphocytic leukemia, multiple myeloma, melanoma, oesophageal cancer, myeloma, hepatocellular, pancreatic, cervical cancer, Ewings sarcoma, neuroblastoma, Kaposi sarcoma, ovarian cancer, breast cancer including secretory breast cancer, colorectal 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 and leukaemia; particularly ovarian cancer, breast cancer, colorectal cancer, prostate cancer and lung cancer - NSCLC and SCLC; more particularly prostate cancer; and more particularly hormone refractory prostate cancer.

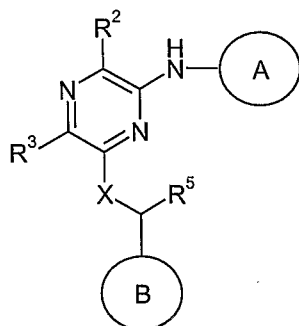
The compounds of Formula (I) are also believed to possess JAK kinase inhibitory activity and are accordingly useful for their anti-proliferation and/or pro-apoptotic activity and in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said compound, 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 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.

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, 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; particularly myeloma, leukemia, ovarian cancer, breast cancer and prostate cancer.

The present invention provides a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is selected from the group consisting of 5- and 6- membered heteroaryl, wherein said 5- and 6- membered heteroaryl are optionally substituted with one or more R^1 ;

Ring B is selected from the group consisting of carbocyclyl and heterocyclyl, wherein said carbocyclyl and heterocyclyl are optionally substituted with one or more R^6 ;

X is selected from the group consisting of -O-, -S-, and -N(R^{4a})-;

R^1 in each occurrence is independently selected from the group consisting of halo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, heterocyclyl, -OR^{1a}, -SR^{1a}, -N(R^{1a})₂, -N(R^{1a})C(O)R^{1b}, -N(R^{1a})N(R^{1a})₂, -NO₂, -C(O)H, -C(O)R^{1b}, -C(O)₂R^{1a}, -C(O)N(R^{1a})₂, -OC(O)N(R^{1a})₂, -N(R^{1a})C(O)₂R^{1a}, -N(R^{1a})C(O)N(R^{1a})₂, -OC(O)R^{1b}, -S(O)R^{1b}, -S(O)₂R^{1b}, -S(O)₂N(R^{1a})₂, -N(R^{1a})S(O)₂R^{1b}, -C(R^{1a})=N(R^{1a}), and -C(R^{1a})=N(OR^{1a}), wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R^{10} ;

R^{1a} in each occurrence is independently selected from the group consisting of H, C_{1-6} alkyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^{10} ;

R^{1b} in each occurrence is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^{10} ;

R^2 is selected from the group consisting of H, halo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} 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, -NO₂, -C(O)H, -C(O)R^{2b}, -C(O)₂R^{2a}, -C(O)N(R^{2a})₂, -OC(O)N(R^{2a})₂, -N(R^{2a})C(O)₂R^{2a}, -N(R^{2a})C(O)N(R^{2a})₂, -OC(O)R^{2b}, -S(O)R^{2b}, -S(O)₂R^{2b}, -S(O)₂N(R^{2a})₂, -N(R^{2a})S(O)₂R^{2b}, -C(R^{2a})=N(R^{2a}), and -C(R^a)=N(OR^{2a}), wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R^{20} ;

R^{2a} in each occurrence is independently selected from the group consisting of H, C_{1-6} alkyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R^{20} ;

R^{2b} in each occurrence is independently selected from the group consisting of C_{1-6} alkyl,

C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R²⁰;

R³ is selected from the group consisting of H, halo, -CN, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, heterocyclyl, -OR^{3a}, -SR^{3a}, -N(R^{3a})₂, -N(R^{3a})C(O)R^{3b}, -N(R^{3a})N(R^{3a})₂, -NO₂, -C(O)H, -C(O)R^{3b}, -C(O)₂R^{3a}, -C(O)N(R^{3a})₂, -OC(O)N(R^{3a})₂, -N(R^{3a})C(O)₂R^{3a}, -N(R^{3a})C(O)N(R^{3a})₂, -OC(O)R^{3b}, -S(O)R^{3b}, -S(O)₂R^{3b}, -S(O)₂N(R^{3a})₂, -N(R^{3a})S(O)₂R^{3b}, -C(R^{3a})=N(R^{3a}), and -C(R^{3a})=N(OR^{3a}), wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R³⁰;

R^{3a} in each occurrence is independently selected from the group consisting of H, C₁₋₆alkyl, carbocyclyl, and heterocyclyl, wherein said C₁₋₆alkyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R³⁰;

R^{3b} in each occurrence is independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R³⁰;

R^{4a} is selected from the group consisting of H, C₁₋₆alkyl, carbocyclyl, and heterocyclyl, wherein said C₁₋₆alkyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R⁴⁰;

R⁵ is selected from the group consisting of -CN, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, heterocyclyl, -N(R^{5a})C(O)R^{5b}, -N(R^{5a})N(R^{5a})₂, -NO₂, -C(O)H, -C(O)R^{5b}, -C(O)₂R^{5a}, -C(O)N(R^{5a})₂, -OC(O)N(R^{5a})₂, -N(R^{5a})C(O)₂R^{5a}, -N(R^{5a})C(O)N(R^{5a})₂, -OC(O)R^{5b}, -S(O)R^{5b}, -S(O)₂R^{5b}, -S(O)₂N(R^{5a})₂, -N(R^{5a})S(O)₂R^{5b}, -C(R^{5a})=N(R^{5a}), and -C(R^{5a})=N(OR^{5a}), wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R⁵⁰;

R^{5a} in each occurrence is independently selected from the group consisting of H, C₁₋₆alkyl, carbocyclyl, and heterocyclyl, wherein said C₁₋₆alkyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R⁵⁰;

R^{5b} in each occurrence is independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R⁵⁰;

R^6 in each occurrence is independently selected from the group consisting of halo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, heterocyclyl, $-OR^{6a}$, $-SR^{6a}$, $-N(R^{6a})_2$, $-N(R^{6a})C(O)R^{6b}$, $-N(R^{6a})N(R^{6a})_2$, $-NO_2$, $-C(O)H$, $-C(O)R^{6b}$, $-C(O)_2R^{6a}$, $-C(O)N(R^{6a})_2$, $-OC(O)N(R^{6a})_2$, $-N(R^{6a})C(O)_2R^{6a}$, $-N(R^{6a})C(O)N(R^{6a})_2$, $-OC(O)R^{6b}$, $-S(O)R^{6b}$, $-S(O)_2R^{6b}$, $-S(O)_2N(R^{6a})_2$, $-N(R^{6a})S(O)_2R^{6b}$, $-C(R^{6a})=N(R^{6a})$, and $-C(R^{6a})=N(OR^{6a})$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R^{60} ;

R^{6a} in each occurrence is independently selected from the group consisting of H, C_{1-6} alkyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^{60} ;

R^{6b} in each occurrence is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^{60} ;

R^{10} in each occurrence is independently selected from the group consisting of halo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, heterocyclyl, $-OR^{10a}$, $-SR^{10a}$, $-N(R^{10a})_2$, $-N(R^{10a})C(O)R^{10b}$, $-N(R^{10a})N(R^{10a})_2$, $-NO_2$, $-C(O)H$, $-C(O)R^{10b}$, $-C(O)_2R^{10a}$, $-C(O)N(R^{10a})_2$, $-OC(O)N(R^{10a})_2$, $-N(R^{10a})C(O)_2R^{10a}$, $-N(R^{10a})C(O)N(R^{10a})_2$, $-OC(O)R^{10b}$, $-S(O)R^{10b}$, $-S(O)_2R^{10b}$, $-S(O)_2N(R^{10a})_2$, $-N(R^{10a})S(O)_2R^{10b}$, $-C(R^{10a})=N(R^{10a})$, and $-C(R^{10a})=N(OR^{10a})$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^a ;

R^{10a} in each occurrence is independently selected from the group consisting of H, C_{1-6} alkyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^a ;

R^{10b} in each occurrence is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^a ;

R^{20} in each occurrence is independently selected from the group consisting of halo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, heterocyclyl, $-OR^{20a}$, $-SR^{20a}$, $-N(R^{20a})_2$, $-N(R^{20a})C(O)R^{20b}$, $-N(R^{20a})N(R^{20a})_2$, $-NO_2$, $-C(O)H$, $-C(O)R^{20b}$, $-C(O)_2R^{20a}$, $-C(O)N(R^{20a})_2$,

$-\text{OC}(\text{O})\text{N}(\text{R}^{20\text{a}})_2$, $-\text{N}(\text{R}^{20\text{a}})\text{C}(\text{O})_2\text{R}^{20\text{a}}$, $-\text{N}(\text{R}^{20\text{a}})\text{C}(\text{O})\text{N}(\text{R}^{20\text{a}})_2$, $-\text{OC}(\text{O})\text{R}^{20\text{b}}$, $-\text{S}(\text{O})\text{R}^{20\text{b}}$, $-\text{S}(\text{O})_2\text{R}^{20\text{b}}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{20\text{a}})_2$, $-\text{N}(\text{R}^{20\text{a}})\text{S}(\text{O})_2\text{R}^{20\text{b}}$, $-\text{C}(\text{R}^{20\text{a}})=\text{N}(\text{R}^{20\text{a}})$, and $-\text{C}(\text{R}^{20\text{a}})=\text{N}(\text{OR}^{20\text{a}})$, wherein said $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^{b} ;

$\text{R}^{20\text{a}}$ in each occurrence is independently selected from the group consisting of H, $\text{C}_{1-6}\text{alkyl}$, carbocyclyl, and heterocyclyl, wherein said $\text{C}_{1-6}\text{alkyl}$, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^{b} ;

$\text{R}^{20\text{b}}$ in each occurrence is independently selected from the group consisting of $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, carbocyclyl, and heterocyclyl, wherein said $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^{b} ;

R^{30} in each occurrence is independently selected from the group consisting of halo, $-\text{CN}$, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, carbocyclyl, heterocyclyl, $-\text{OR}^{30\text{a}}$, $-\text{SR}^{30\text{a}}$, $-\text{N}(\text{R}^{30\text{a}})_2$, $-\text{N}(\text{R}^{30\text{a}})\text{C}(\text{O})\text{R}^{30\text{b}}$, $-\text{N}(\text{R}^{30\text{a}})\text{N}(\text{R}^{30\text{a}})_2$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})\text{R}^{30\text{b}}$, $-\text{C}(\text{O})_2\text{R}^{30\text{a}}$, $-\text{C}(\text{O})\text{N}(\text{R}^{30\text{a}})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{30\text{a}})_2$, $-\text{N}(\text{R}^{30\text{a}})\text{C}(\text{O})_2\text{R}^{30\text{a}}$, $-\text{N}(\text{R}^{30\text{a}})\text{C}(\text{O})\text{N}(\text{R}^{30\text{a}})_2$, $-\text{OC}(\text{O})\text{R}^{30\text{b}}$, $-\text{S}(\text{O})\text{R}^{30\text{b}}$, $-\text{S}(\text{O})_2\text{R}^{30\text{b}}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{30\text{a}})_2$, $-\text{N}(\text{R}^{30\text{a}})\text{S}(\text{O})_2\text{R}^{30\text{b}}$, $-\text{C}(\text{R}^{30\text{a}})=\text{N}(\text{R}^{30\text{a}})$, and $-\text{C}(\text{R}^{30\text{a}})=\text{N}(\text{OR}^{30\text{a}})$, wherein said $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^{c} ;

$\text{R}^{30\text{a}}$ in each occurrence is independently selected from the group consisting of H, $\text{C}_{1-6}\text{alkyl}$, carbocyclyl, and heterocyclyl, wherein said $\text{C}_{1-6}\text{alkyl}$, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^{c} ;

$\text{R}^{30\text{b}}$ in each occurrence is independently selected from the group consisting of $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, carbocyclyl, and heterocyclyl, wherein said $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^{c} ;

R^{40} in each occurrence is independently selected from the group consisting of halo, $-\text{CN}$, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, carbocyclyl, heterocyclyl, $-\text{OR}^{40\text{a}}$, $-\text{SR}^{40\text{a}}$, $-\text{N}(\text{R}^{40\text{a}})_2$, $-\text{N}(\text{R}^{40\text{a}})\text{C}(\text{O})\text{R}^{40\text{b}}$, $-\text{N}(\text{R}^{40\text{a}})\text{N}(\text{R}^{40\text{a}})_2$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})\text{R}^{40\text{b}}$, $-\text{C}(\text{O})_2\text{R}^{40\text{a}}$, $-\text{C}(\text{O})\text{N}(\text{R}^{40\text{a}})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{40\text{a}})_2$, $-\text{N}(\text{R}^{40\text{a}})\text{C}(\text{O})_2\text{R}^{40\text{a}}$, $-\text{N}(\text{R}^{40\text{a}})\text{C}(\text{O})\text{N}(\text{R}^{40\text{a}})_2$, $-\text{OC}(\text{O})\text{R}^{40\text{b}}$, $-\text{S}(\text{O})\text{R}^{40\text{b}}$, $-\text{S}(\text{O})_2\text{R}^{40\text{b}}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{40\text{a}})_2$, $-\text{N}(\text{R}^{40\text{a}})\text{S}(\text{O})_2\text{R}^{40\text{b}}$, $-\text{C}(\text{R}^{40\text{a}})=\text{N}(\text{R}^{40\text{a}})$, and $-\text{C}(\text{R}^{40\text{a}})=\text{N}(\text{OR}^{40\text{a}})$, wherein said $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, carbocyclyl, and heterocyclyl are each independently and

optionally substituted with one or more R^d ;

R^{40a} in each occurrence is independently selected from the group consisting of H, C_{1-6} alkyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^d ;

R^{40b} in each occurrence is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^d ;

R^{50} in each occurrence is independently selected from the group consisting of halo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, heterocyclyl, $-OR^{50a}$, $-SR^{50a}$, $-N(R^{50a})_2$, $-N(R^{50a})C(O)R^{50b}$, $-N(R^{50a})N(R^{50a})_2$, $-NO_2$, $-C(O)H$, $-C(O)R^{50b}$, $-C(O)_2R^{50a}$, $-C(O)N(R^{50a})_2$, $-OC(O)N(R^{50a})_2$, $-N(R^{50a})C(O)_2R^{50a}$, $-N(R^{50a})C(O)N(R^{50a})_2$, $-OC(O)R^{50b}$, $-S(O)R^{50b}$, $-S(O)_2R^{50b}$, $-S(O)_2N(R^{50a})_2$, $-N(R^{50a})S(O)_2R^{50b}$, $-C(R^{50a})=N(R^{50a})$, and $-C(R^{50a})=N(OR^{50a})$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^e ;

R^{50a} in each occurrence is independently selected from the group consisting of H, C_{1-6} alkyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^e ;

R^{50b} in each occurrence is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^e ;

R^{60} in each occurrence is independently selected from the group consisting of halo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, heterocyclyl, $-OR^{60a}$, $-SR^{60a}$, $-N(R^{60a})_2$, $-N(R^{60a})C(O)R^{60b}$, $-N(R^{60a})N(R^{60a})_2$, $-NO_2$, $-C(O)H$, $-C(O)R^{60b}$, $-C(O)_2R^{60a}$, $-C(O)N(R^{60a})_2$, $-OC(O)N(R^{60a})_2$, $-N(R^{60a})C(O)_2R^{60a}$, $-N(R^{60a})C(O)N(R^{60a})_2$, $-OC(O)R^{60b}$, $-S(O)R^{60b}$, $-S(O)_2R^{60b}$, $-S(O)_2N(R^{60a})_2$, $-N(R^{60a})S(O)_2R^{60b}$, $-C(R^{60a})=N(R^{60a})$, and $-C(R^{60a})=N(OR^{60a})$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^f ;

R^{60a} in each occurrence is independently selected from the group consisting of H, C_{1-6} alkyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, carbocyclyl, and heterocyclyl are each

independently and optionally substituted with one or more R^f ;

R^{60b} in each occurrence is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^f ;

R^a , R^b , R^c , R^d , R^e , and R^f in each occurrence are independently selected from the group consisting of halo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, heterocyclyl, -OR^m, -SR^m, -N(R^m)₂, -N(R^m)C(O)Rⁿ, -N(R^m)N(R^m)₂, -NO₂, -C(O)H, -C(O)Rⁿ, -C(O)₂R^m, -C(O)N(R^m)₂, -OC(O)N(R^m)₂, -N(R^m)C(O)₂R^m, -N(R^m)C(O)N(R^m)₂, -OC(O)Rⁿ, -S(O)Rⁿ, -S(O)₂Rⁿ, -S(O)₂N(R^m)₂, -N(R^m)S(O)₂Rⁿ, -C(R^m)=N(R^m), and -C(R^m)=N(OR^m);

R^m in each occurrence is independently selected from the group consisting of H and C_{1-6} alkyl; and

R^n in each occurrence is C_{1-6} alkyl.

Detailed Description of the Invention

In this specification the prefix C_{x-y} as used in terms such as C_{x-y} 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, C_{1-4} alkyl includes C_1 alkyl (methyl), C_2 alkyl (ethyl), C_3 alkyl (propyl and isopropyl) and C_4 alkyl (butyl, 1-methylpropyl, 2-methylpropyl, and *t*-butyl).

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.

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, “ C_{2-6} alkenyl” includes, but is not limited to, groups such as C_{2-6} alkenyl, C_{2-4} alkenyl, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, and 2-methyl-1-heptenyl.

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-butyne, 4-pentyne, 5-hexyne, 2-heptyne, and 4-methyl-5-heptyne.

The term “halo” refers to fluoro, chloro, bromo and iodo.

The term “carbocyclyl” refers to a saturated, partially saturated, or unsaturated, mono or bicyclic carbon ring that contains 3 to 12 ring atoms, wherein one or more -CH₂- groups may optionally be replaced by a corresponding number of -C(O)- groups. In one aspect, the term “carbocyclyl” may refer to a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Illustrative examples of “carbocyclyl” include, but are not limited to, adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, indanyl, naphthyl, 1-oxocyclopentyl, 1-oxoindanyl, phenyl, and tetralinyl. In one aspect, the term “carbocyclyl” may refer to a saturated carbocyclyl ring, i.e. a ring of carbon atoms in which the carbon-carbon bonds are single bonds.

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 atom is chosen from nitrogen, sulfur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein 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, imidazolyl, indolyl, isoquinolone, isothiazolyl, isoxazolyl, morpholino, 2-oxopyrrolidinyl, 2-oxo-1,3-thiazolidinyl, piperazinyl, piperidyl, pyranyl, pyrazolyl, pyridinyl, pyrrolyl, pyrrolidinyl, pyrrolinyl, pyrimidyl, pyrazinyl, pyrazolyl, pyridazinyl, 4-pyridonyl, quinolyl, tetrahydropyranyl, thiazolyl, thiadiazolyl, thiazolidinyl, thiomorpholino, thiophenyl, pyridine-*N*-oxide and quinoline-*N*-oxide.

In one aspect, the term “heterocyclyl” may refer to a saturated, partially saturated, or unsaturated, monocyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulfur or oxygen, and may, unless otherwise specified, be carbon or nitrogen linked, and a ring nitrogen atom may be optionally oxidized to form an N-oxide. 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, 2*H*-pyranyl, pyrazolyl, pyridinyl, pyrrolyl, pyrrolidinyl, pyrrolidinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyridazinyl, 4-pyridonyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolyl, thiadiazolyl, thiazolidinyl, thiomorpholino, thiophenyl, and pyridine-*N*-oxidyl.

In another aspect, the term “heterocyclyl” may refer to “heteroaryl” groups. The term “heteroaryl” is intended to refer to those mono or bicyclic heterocyclyl groups of which at least one ring is aromatic. Illustrative examples of the term “heteroaryl” include, but are not limited to, benzofuranyl, cinnolinyl, furanyl, indolyl, isoquinolinyl, isoxazolyl, 2-oxa-5-azabicyclo[2.2.1]hept-5-yl, oxazolyl, pyrazolyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyridinyl, pyrrolyl, quinolinyl, quinoxalinyl, thiazolyl, and thiophenyl.

In one aspect, the term “heteroaryl” may refer to a 5- or 6-membered heteroaryl group. In another aspect, the term “heteroaryl” may refer to a 5-membered heteroaryl group. Illustrative examples of the term “5-membered heteroaryl” include, but are not limited to, imidazolyl, oxazolyl, pyrrolyl, thiazolyl, and thiophenyl. In still another aspect, the term “heteroaryl” may refer to a 6-membered heteroaryl group.

Where a particular R group (e.g. R^{1a}, R¹⁰, 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, C₁₋₆alkyl; 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.

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.

The term "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.

The term "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, that particular group is unsubstituted. In another aspect, the particular group bears one substituent. In another aspect, the particular substituent bears two substituents. In still another aspect, the particular group bears three substituents. In yet another aspect, the particular group bears four substituents. In a further aspect, the particular group bears one or two substituents. In still a further aspect, the particular group bears zero to two substituents.

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.

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.

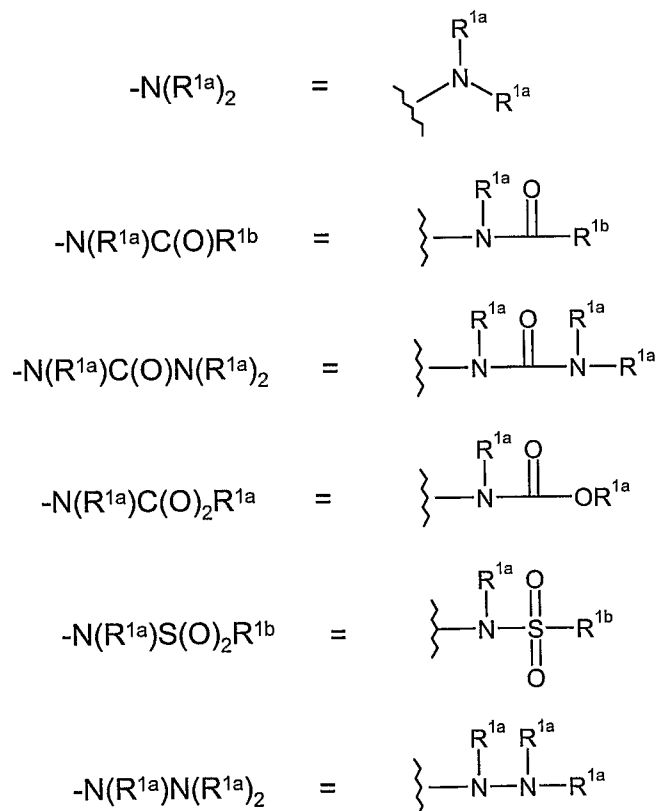
Illustrative examples of suitable protecting groups for a hydroxy group include, but are not limited to, an acyl group; alkanoyl groups such as acetyl; aroyl groups, such as benzoyl; silyl groups, such as trimethylsilyl; and arylmethyl groups, such as benzyl. The deprotection conditions for the above 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.

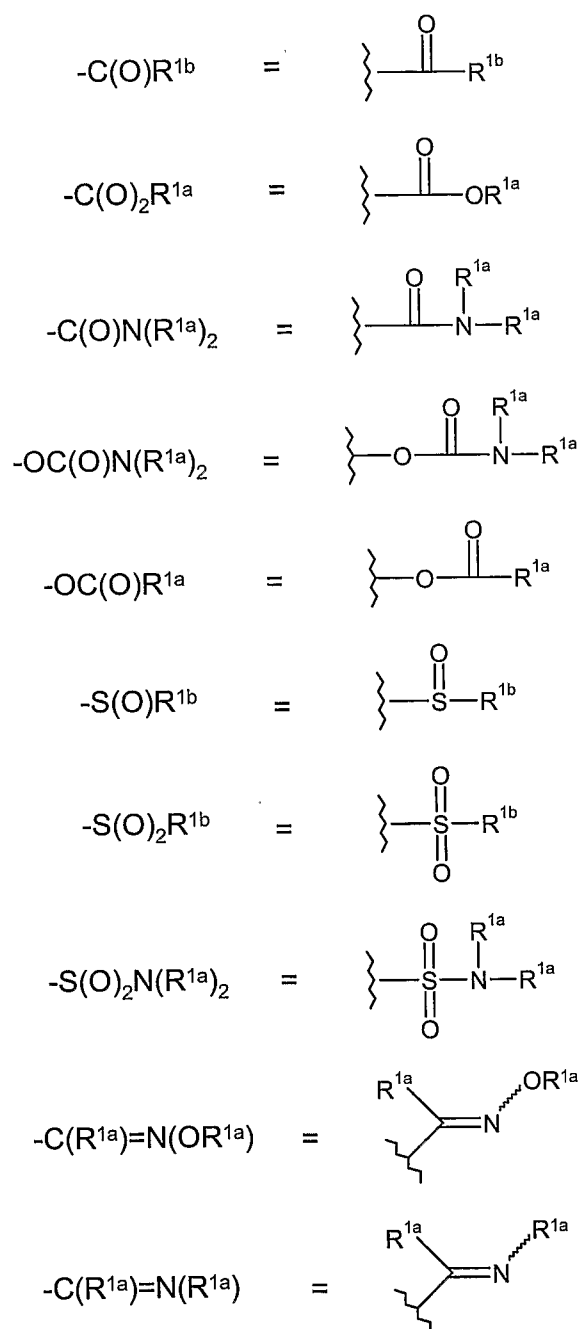
Illustrative examples of suitable protecting groups for an amino group include, but are not limited to, acyl groups; alkanoyl groups such as acetyl; alkoxycarbonyl groups, such as methoxycarbonyl, ethoxycarbonyl, and *t*-butoxycarbonyl; arylmethoxycarbonyl groups, such as benzyloxycarbonyl; and aroyl groups, such as 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 alkoxycarbonyl 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 benzyloxycarbonyl

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:





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 such acid addition salts include acetate, adipate, ascorbate, benzoate, benzenesulfonate, bicarbonate, bisulfate, butyrate, camphorate, 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. 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, 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; aralkyl halides such as benzyl bromide and others. Non-toxic physiologically-acceptable salts are preferred, although other salts are also 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

In one aspect, **Ring A** may be selected from 5- and 6-membered heteroaryl, wherein said 5- and 6-membered heteroaryl may be optionally substituted with one or more R^1 ;

R^1 in each occurrence may be independently selected from -CN, C_{1-6} alkyl, $-OR^{1a}$, and saturated carbocyclyl; and

R^{1a} may be C_{1-6} alkyl.

In another aspect, **Ring A** may be selected from 5-membered heteroaryl, wherein said 5-membered heteroaryl may be optionally substituted with one or more R^1 ;

R^1 in each occurrence may be independently selected from -CN, C_{1-6} alkyl, $-OR^{1a}$, and saturated carbocyclyl; and

R^{1a} may be C_{1-6} alkyl.

In still another aspect, **Ring A** may be selected from 5-membered heteroaryl, wherein said 5-membered heteroaryl may be optionally substituted with one or more R^1 ;

R^1 in each occurrence may be independently selected from -CN, C_{1-6} alkyl, $-OR^{1a}$, and cyclopropyl; and

R^{1a} may be C_{1-6} alkyl.

In yet another aspect, **Ring A** may be 5-membered heteroaryl, wherein said 5-membered heteroaryl may be optionally substituted with one or more R^1 ;

R^1 in each occurrence may be independently selected from C_{1-6} alkyl and $-OR^{1a}$; and

R^{1a} may be C₁₋₆alkyl.

In a further aspect, **Ring A** may be 5-membered heteroaryl, wherein said 5-membered heteroaryl may be optionally substituted on carbon with one or more **R¹**;

R¹ in each occurrence may be independently selected from C₁₋₆alkyl, -OR^{1a}, and saturated carbocyclyl; and

R^{1a} may be C₁₋₆alkyl.

In still a further aspect, **Ring A** may be 5-membered heteroaryl containing 1 or 2 heteroatoms selected from N and S, wherein said 5-membered heteroaryl may be optionally substituted with one or more **R¹**;

R¹ in each occurrence may be independently selected from C₁₋₆alkyl and -OR^{1a}; and

R^{1a} may be C₁₋₆alkyl.

In yet a further another aspect, **Ring A** may be selected from pyrazolyl and thiazolyl, wherein said pyrazolyl and thiazolyl may be optionally substituted with one or more **R¹**;

R¹ in each occurrence may be independently selected from -CN, C₁₋₆alkyl, -OR^{1a}, and saturated carbocyclyl; and

R^{1a} may be C₁₋₆alkyl.

In one aspect, **Ring A** may be selected from pyrazolyl and thiazolyl, wherein said pyrazolyl and thiazolyl may be optionally substituted with one or more **R¹**;

R¹ in each occurrence may be independently selected from C₁₋₆alkyl and -OR^{1a}; and

R^{1a} may be C₁₋₆alkyl.

In another aspect, **Ring A** may be selected from pyrazolyl and thiazolyl, wherein said pyrazolyl and thiazolyl may be optionally substituted on carbon with one or more **R¹**;

R¹ in each occurrence may be independently selected from C₁₋₆alkyl, -OR^{1a}, and cyclopropyl; and

R^{1a} may be C₁₋₆alkyl.

In still another aspect, **Ring A** may be pyrazolyl, wherein said pyrazolyl may be optionally substituted with one or more R^1 ; and

R^1 in each occurrence may be independently selected from methyl and methoxy.

In yet another a further aspect, **Ring A** may be pyrazolyl, wherein said pyrazolyl may be optionally substituted with one or more R^1 ; and

R^1 in each occurrence may be independently selected from methyl, methoxy, isopropoxy, and cyclopropyl.

In a further aspect, **Ring A** may be thiazolyl, wherein said thiazolyl may be optionally substituted with one or more R^1 ; and

R^1 in each occurrence may be independently selected from methyl and methoxy.

In still a further another aspect, **Ring A** may be thiazolyl, wherein said thiazolyl may be optionally substituted with one or more R^1 ; and

R^1 in each occurrence may be independently selected from methyl, methoxy, and cyano.

In yet a further aspect, **Ring A** may be selected from 5-methyl-1*H*-pyrazol-3-yl, 5-methoxy-1*H*-pyrazol-3-yl, 5-methyl-thiazol-2-yl, and 5-amino-2-cyano-1,3-thiazol-4-yl.

In one aspect, **Ring A** may be selected from 5-methyl-1*H*-pyrazol-3-yl, 5-methoxy-1*H*-pyrazol-3-yl, and 5-methyl-thiazol-2-yl.

In another aspect, **Ring A** may be selected from 5-cyclopropyl-1*H*-pyrazol-3-yl, 5-isopropoxy-1*H*-pyrazol-3-yl, 5-methyl-1*H*-pyrazol-3-yl, 5-methoxy-1*H*-pyrazol-3-yl, and 5-methyl-thiazol-2-yl.

In still another aspect, **Ring A** may be selected from 5-methyl-1*H*-pyrazol-3-yl, and 5-methoxy-1*H*-pyrazol-3-yl.

In yet another aspect, **Ring A** may be selected from 5-cyclopropyl-1*H*-pyrazol-3-yl, 5-isopropoxy-1*H*-pyrazol-3-yl, 5-methyl-1*H*-pyrazol-3-yl, and 5-methoxy-1*H*-pyrazol-3-yl.

In a further aspect, **Ring A** may be 5-methyl-thiazol-2-yl.

In still a further aspect, **Ring A** may be 5-methoxy-1*H*-pyrazol-3-yl.

Ring B

In one aspect, **Ring B** may be selected from phenyl and 5- and 6-membered heteroaryl, wherein said phenyl and 5- and 6-membered heteroaryl may be optionally substituted with one or more R^6 ; and R^6 may be halo.

In another aspect, **Ring B** may be selected from phenyl and 6-membered heteroaryl, wherein said phenyl and 5- and 6-membered heteroaryl may be optionally substituted with one or more R^6 ; and R^6 may be halo.

In still another aspect, **Ring B** may be 6-membered heteroaryl, wherein said 6-membered heteroaryl may be optionally substituted with one or more R^6 ; and R^6 may be halo.

In yet another aspect, **Ring B** may be selected from phenyl, pyridinyl, and pyrimidinyl, wherein said phenyl, pyridinyl, and pyrimidinyl may be optionally substituted with one or more R^6 ; and R^6 may be halo.

In a further aspect, **Ring B** may be selected from phenyl, pyridinyl, and pyrimidinyl, wherein said phenyl, pyridinyl, and pyrimidinyl may be optionally substituted with one or more R^6 ; and R^6 may be fluoro.

In still a further aspect, **Ring B** may be phenyl, wherein said phenyl may be optionally substituted with one or more R^6 ; and R^6 may be halo.

In yet a further aspect, **Ring B** may be pyridinyl, wherein said phenyl may be optionally substituted with one or more R^6 ; and R^6 may be halo.

In one aspect, **Ring B** may be pyrimidinyl, wherein said pyrimidinyl may be optionally substituted with R^6 ; and R^6 may be halo.

In another aspect, **Ring B** may be selected from 4-fluorophenyl, 5-fluoropyridin-2-yl, and 4-fluorophenylpyrimidin-2-yl.

In still another aspect, **Ring B** may be selected from 3,5-difluoropyridin-2-yl, 4-fluorophenyl, 5-fluoropyridin-2-yl, and 4-fluorophenylpyrimidin-2-yl.

In yet another aspect, **Ring B** may be 4-fluorophenyl.

In a further another aspect, **Ring B** may be 5-fluoropyridin-2-yl.

In still a further aspect, **Ring B** may be 4-fluorophenylpyrimidin-2-yl.

X

In one aspect, **X** may be selected from -NH- and -O-.

In another aspect, **X** may be -NH-.

R²

In one aspect, R^2 may be selected from H and C₁₋₆alkyl.

In another aspect, R^2 may be H.

In still another aspect, R^2 may be C_{1-6} alkyl.

In yet another aspect, R^2 may be selected from H and methyl.

In a further aspect, R^2 may be methyl.

R^3

In one aspect, R^3 may be selected from H and -CN.

In another aspect, R^3 may be H.

In still another aspect, R^3 may be -CN.

R^5

In one aspect, R^5 may be C_{1-6} alkyl, wherein said C_{1-6} alkyl may be optionally substituted with one or more $-OR^{50}$; and

R^{50} may be C_{1-6} alkyl.

In another aspect, R^5 may be C_{1-6} alkyl.

In another aspect, R^5 may be methyl.

Ring A, Ring B, X, R^2 , R^3 , and R^5

In one aspect, **Ring A** may be 5-membered heteroaryl, wherein said 5-membered heteroaryl may be optionally substituted on carbon with one or more R^1 ;

Ring B may be selected from the group consisting of carbocyclyl and heterocyclyl, wherein said carbocyclyl and heterocyclyl may be optionally substituted with one or more R^6 ;

X may be selected from $-N(R^{4a})-$ and $-O-$;

R¹ in each occurrence may be independently selected from the group consisting of halo, -CN, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, heterocyclyl, -OR^{1a}, -SR^{1a}, -N(R^{1a})₂, -N(R^{1a})C(O)R^{1b}, -N(R^{1a})N(R^{1a})₂, -NO₂, -C(O)H, -C(O)R^{1b}, -C(O)₂R^{1a}, -C(O)N(R^{1a})₂, -OC(O)N(R^{1a})₂, -N(R^{1a})C(O)₂R^{1a}, -N(R^{1a})C(O)N(R^{1a})₂, -OC(O)R^{1b}, -S(O)R^{1b}, -S(O)₂R^{1b}, -S(O)₂N(R^{1a})₂, -N(R^{1a})S(O)₂R^{1b}, -C(R^{1a})=N(R^{1a}), and -C(R^{1a})=N(OR^{1a});

R^{1a} in each occurrence may be independently selected from the group consisting of H, C₁₋₆alkyl, carbocyclyl, and heterocyclyl;

R^{1b} in each occurrence may be selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl;

R² may be selected from the group consisting of H, halo, -CN, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, heterocyclyl, -OR^{2a}, -SR^{2a}, -N(R^{2a})₂, -N(R^{2a})C(O)R^{2b}, -N(R^{2a})N(R^{2a})₂, -NO₂, -C(O)H, -C(O)R^{2b}, -C(O)₂R^{2a}, -C(O)N(R^{2a})₂, -OC(O)N(R^{2a})₂, -N(R^{2a})C(O)₂R^{2a}, -N(R^{2a})C(O)N(R^{2a})₂, -OC(O)R^{2b}, -S(O)R^{2b}, -S(O)₂R^{2b}, -S(O)₂N(R^{2a})₂, -N(R^{2a})S(O)₂R^{2b}, -C(R^{2a})=N(R^{2a}), and -C(R^{2a})=N(OR^{2a});

R^{2a} in each occurrence may be independently selected from the group consisting of H, C₁₋₆alkyl, carbocyclyl, and heterocyclyl;

R^{2b} in each occurrence may be independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl may be optionally substituted with one or more R²⁰;

R³ may be selected from the group consisting of H, halo, -CN, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, heterocyclyl, -OR^{3a}, -SR^{3a}, -N(R^{3a})₂, -N(R^{3a})C(O)R^{3b}, -N(R^{3a})N(R^{3a})₂, -NO₂, -C(O)H, -C(O)R^{3b}, -C(O)₂R^{3a}, -C(O)N(R^{3a})₂, -OC(O)N(R^{3a})₂, -N(R^{3a})C(O)₂R^{3a}, -N(R^{3a})C(O)N(R^{3a})₂, -OC(O)R^{3b}, -S(O)R^{3b}, -S(O)₂R^{3b}, -S(O)₂N(R^{3a})₂, -N(R^{3a})S(O)₂R^{3b}, -C(R^{3a})=N(R^{3a}), and -C(R^{3a})=N(OR^{3a});

R^{3a} in each occurrence may be independently selected from the group consisting of H, C₁₋₆alkyl, carbocyclyl, and heterocyclyl;

R^{3b} in each occurrence may be independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl;

R^{4a} may be selected from the group consisting of H, C₁₋₆alkyl, carbocyclyl, and heterocyclyl;

R⁵ may be selected from the group consisting of -CN, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, heterocyclyl, -N(R^{5a})C(O)R^{5b}, -N(R^{5a})N(R^{5a})₂, -NO₂, -C(O)H, -C(O)R^{5b}, -C(O)₂R^{5a},

$-\text{C}(\text{O})\text{N}(\text{R}^{5a})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{5a})_2$, $-\text{N}(\text{R}^{5a})\text{C}(\text{O})_2\text{R}^{5a}$, $-\text{N}(\text{R}^{5a})\text{C}(\text{O})\text{N}(\text{R}^{5a})_2$, $-\text{OC}(\text{O})\text{R}^{5b}$, $-\text{S}(\text{O})\text{R}^{5b}$, $-\text{S}(\text{O})_2\text{R}^{5b}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{5a})_2$, $-\text{N}(\text{R}^{5a})\text{S}(\text{O})_2\text{R}^{5b}$, $-\text{C}(\text{R}^{5a})=\text{N}(\text{R}^{5a})$, and $-\text{C}(\text{R}^{5a})=\text{N}(\text{OR}^{5a})$;

R^{5a} in each occurrence may be independently selected from the group consisting of H, C_{1-6} alkyl, carbocyclyl, and heterocyclyl;

R^{5b} in each occurrence may be independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl;

R^6 in each occurrence may be independently selected from the group consisting of halo, $-\text{CN}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, heterocyclyl, $-\text{OR}^{6a}$, $-\text{SR}^{6a}$, $-\text{N}(\text{R}^{6a})_2$, $-\text{N}(\text{R}^{6a})\text{C}(\text{O})\text{R}^{6b}$, $-\text{N}(\text{R}^{6a})\text{N}(\text{R}^{6a})_2$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})\text{R}^{6b}$, $-\text{C}(\text{O})_2\text{R}^{6a}$, $-\text{C}(\text{O})\text{N}(\text{R}^{6a})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{6a})_2$, $-\text{N}(\text{R}^{6a})\text{C}(\text{O})_2\text{R}^{6a}$, $-\text{N}(\text{R}^{6a})\text{C}(\text{O})\text{N}(\text{R}^{6a})_2$, $-\text{OC}(\text{O})\text{R}^{6b}$, $-\text{S}(\text{O})\text{R}^{6b}$, $-\text{S}(\text{O})_2\text{R}^{6b}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{6a})_2$, $-\text{N}(\text{R}^{6a})\text{S}(\text{O})_2\text{R}^{6b}$, $-\text{C}(\text{R}^{6a})=\text{N}(\text{R}^{6a})$, and $-\text{C}(\text{R}^{6a})=\text{N}(\text{OR}^{6a})$;

R^{6a} in each occurrence may be independently selected from the group consisting of H, C_{1-6} alkyl, carbocyclyl, and heterocyclyl; and

R^{6b} in each occurrence may be independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl.

In another aspect, **Ring A** may be selected from 5- and 6-membered heteroaryl, wherein said 5- and 6-membered heteroaryl may be optionally substituted with one or more R^1 ;

Ring B may be selected from phenyl and 5- and 6-membered heteroaryl, wherein said phenyl and 5- and 6-membered heteroaryl may be optionally substituted with one or more R^6 ;

X may be $-\text{NH}-$;

R^1 in each occurrence may be independently selected from $-\text{CN}$, C_{1-6} alkyl, $-\text{OR}^{1a}$, and cyclopropyl;

R^{1a} may be C_{1-6} alkyl;

R^2 may be selected from H and C_{1-6} alkyl;

R^3 may be selected from H and $-\text{CN}$;

R^5 may be C_{1-6} alkyl, wherein said C_{1-6} alkyl may be optionally substituted with one or more $-\text{OR}^{50}$;

R^6 may be halo; and

R^{50} may be C_{1-6} alkyl.

In still another aspect, **Ring A** may be selected from 5- and 6-membered heteroaryl, wherein said 5- and 6-membered heteroaryl may be optionally substituted with one or more R^1 ;

Ring B may be selected from phenyl and 5- and 6-membered heteroaryl, wherein said phenyl and 5- and 6-membered heteroaryl may be optionally substituted on carbon with one or more R^6 ;

X may be selected from -NH- and -O-;

R^1 in each occurrence may be independently selected from -CN, C_{1-6} alkyl, $-OR^{1a}$, and cyclopropyl;

R^{1a} may be C_{1-6} alkyl;

R^2 may be selected from H and C_{1-6} alkyl;

R^3 may be selected from H and -CN;

R^5 may be C_{1-6} alkyl, wherein said C_{1-6} alkyl may be optionally substituted with one or more $-OR^{50}$;

R^6 may be halo; and

R^{50} may be C_{1-6} alkyl.

In yet another aspect, **Ring A** may be selected from 5-membered heteroaryl, wherein said 5-membered heteroaryl may be optionally substituted with one or more R^1 ;

Ring B may be selected from phenyl and 6-membered heteroaryl, wherein said phenyl and 6-membered heteroaryl may be optionally substituted with one or more R^6 ;

X may be -NH-

R^1 in each occurrence may be independently selected from -CN, C_{1-6} alkyl, $-OR^{1a}$, and cyclopropyl;

R^{1a} may be C_{1-6} alkyl;

R^2 may be selected from H and C_{1-6} alkyl;

R^3 may be selected from H and -CN;

R^5 may be C_{1-6} alkyl, wherein said C_{1-6} alkyl may be optionally substituted with one or more $-OR^{50}$;

R^6 may be halo; and

R^{50} may be C_{1-6} alkyl.

In a further aspect, **Ring A** may be 5-membered heteroaryl, wherein said 5-membered heteroaryl may be optionally substituted with one or more R^1 ;

Ring B may be selected from phenyl and 5- and 6-membered heteroaryl, wherein said phenyl and

6-membered heteroaryl may be optionally substituted with one or more R⁶;

X may be -NH-

R¹ in each occurrence may be independently selected from C₁₋₆alkyl and -OR^{1a};

R^{1a} may be C₁₋₆alkyl;

R² may be selected from H and C₁₋₆alkyl;

R³ may be selected from H and -CN;

R⁵ may be C₁₋₆alkyl; and

R⁶ may be halo.

In still a further aspect, **Ring A** may be 5-membered heteroaryl, wherein said 5-membered heteroaryl may be optionally substituted on carbon with one or more R¹;

Ring B may be selected from phenyl and 5- and 6-membered heteroaryl, wherein said phenyl and 6-membered heteroaryl may be optionally substituted on carbon with one or more R⁶;

X may be selected from -NH- and -O-;

R¹ in each occurrence may be independently selected from C₁₋₆alkyl, -OR^{1a}, and cyclopropyl;

R^{1a} may be C₁₋₆alkyl;

R² may be selected from H and C₁₋₆alkyl;

R³ may be selected from H and -CN;

R⁵ may be C₁₋₆alkyl; and

R⁶ may be halo.

In yet a further aspect, **Ring A** may be 5-membered heteroaryl, wherein said 5-membered heteroaryl may be optionally substituted with one or more R¹;

Ring B may be selected from phenyl and 5- and 6-membered heteroaryl, wherein said phenyl and 6-membered heteroaryl may be optionally substituted with one or more R⁶;

X may be -NH-

R¹ in each occurrence may be independently selected from C₁₋₆alkyl and -OR^{1a};

R^{1a} may be C₁₋₆alkyl;

R² may be selected from H and C₁₋₆alkyl;

R³ may be selected from H and -CN;

R⁵ may be C₁₋₆alkyl; and

R⁶ may be halo.

In one aspect, **Ring A** may be 5-membered heteroaryl, wherein said 5-membered heteroaryl may be optionally substituted on carbon with one or more **R**¹;

Ring B may be selected from phenyl and 5- and 6-membered heteroaryl, wherein said phenyl and 6-membered heteroaryl may be optionally substituted on carbon with one or more **R**⁶;

X may be selected from -NH- and -O-;

R¹ in each occurrence may be independently selected from C₁₋₆alkyl, -OR^{1a}, and cyclopropyl;

R^{1a} may be C₁₋₆alkyl;

R² may be selected from H and C₁₋₆alkyl;

R³ may be selected from H and -CN;

R⁵ may be C₁₋₆alkyl; and

R⁶ may be halo.

In another aspect, **Ring A** may be 5-membered heteroaryl, wherein said 5-membered heteroaryl may be optionally substituted with one or more **R**¹;

Ring B may be selected from phenyl and 6-membered heteroaryl, wherein said phenyl and 6-membered heteroaryl may be optionally substituted with one or more **R**⁶;

X may be -NH-

R¹ in each occurrence may be independently selected from C₁₋₆alkyl and -OR^{1a};

R^{1a} may be C₁₋₆alkyl;

R² may be selected from H and C₁₋₆alkyl;

R³ may be selected from H and -CN;

R⁵ may be C₁₋₆alkyl; and

R⁶ may be halo.

In still another aspect, **Ring A** may be 5-membered heteroaryl, wherein said 5-membered heteroaryl may be optionally substituted on carbon with one or more **R**¹;

Ring B may be selected from phenyl and 6-membered heteroaryl, wherein said phenyl and 6-membered heteroaryl may be optionally substituted on carbon with one or more **R**⁶;

X may be selected from -NH- and -O-;

R¹ in each occurrence may be independently selected from C₁₋₆alkyl, -OR^{1a}, and cyclopropyl;
R^{1a} may be C₁₋₆alkyl;
R² may be selected from H and C₁₋₆alkyl;
R³ may be selected from H and -CN;
R⁵ may be C₁₋₆alkyl; and
R⁶ may be halo.

In yet another aspect, **Ring A** may be 5-membered heteroaryl, wherein said 5-membered heteroaryl may be optionally substituted with one or more **R**¹;
Ring B may be selected from phenyl and 6-membered heteroaryl, wherein said phenyl and 6-membered heteroaryl may be optionally substituted with one or more **R**⁶;
X may be -NH-;
R¹ in each occurrence may be independently selected from C₁₋₆alkyl and -OR^{1a};
R^{1a} may be C₁₋₆alkyl;
R² may be selected from H and C₁₋₆alkyl;
R³ may be selected from H and -CN;
R⁵ may be C₁₋₆alkyl; and
R⁶ may be halo.

In a further aspect, **Ring A** may be 5-membered heteroaryl, wherein said 5-membered heteroaryl may be optionally substituted on carbon with one or more **R**¹;
Ring B may be selected from phenyl and 6-membered heteroaryl, wherein said phenyl and 6-membered heteroaryl may be optionally substituted on carbon with one or more **R**⁶;
X may be selected from -NH- and -O-;
R¹ in each occurrence may be independently selected from C₁₋₆alkyl, -OR^{1a}, and cyclopropyl;
R^{1a} may be C₁₋₆alkyl;
R² may be selected from H and C₁₋₆alkyl;
R³ may be selected from H and -CN;
R⁵ may be C₁₋₆alkyl; and
R⁶ may be halo.

In a still further aspect, **Ring A** may be selected from pyrazolyl and thiazolyl, wherein said pyrazolyl and thiazolyl may be optionally substituted one or more R¹;

Ring B may be selected from phenyl, pyridinyl, and pyrimidinyl, wherein said phenyl, pyridinyl, and pyrimidinyl may be optionally substituted with one or more R⁶;

X may be -NH-; O

R¹ in each occurrence may be independently selected from -CN, C₁₋₆alkyl, -OR^{1a}, and cyclopropyl;

R^{1a} may be C₁₋₆alkyl;

R² may be selected from H and C₁₋₆alkyl;

R³ may be selected from H and -CN;

R⁵ may be C₁₋₆alkyl; and

R⁶ may be halo.

In yet a further aspect, **Ring A** may be selected from pyrazolyl and thiazolyl, wherein said pyrazolyl and thiazolyl may be optionally substituted with one or more R¹;

Ring B may be selected from phenyl, pyridinyl, and pyrimidinyl, wherein said phenyl, pyridinyl, and pyrimidinyl may be optionally substituted with one or more R⁶;

X may be -NH-;

R¹ in each occurrence may be independently selected from methyl and methoxy;

R² may be selected from H and methyl;

R³ may be selected from H and -CN;

R⁵ may be methyl; and

R⁶ may be fluoro.

In one aspect, **Ring A** may be selected from pyrazolyl and thiazolyl, wherein said pyrazolyl and thiazolyl may be optionally substituted on carbon with one or more R¹;

Ring B may be selected from phenyl, pyridinyl, and pyrimidinyl, wherein said phenyl, pyridinyl, and pyrimidinyl may be optionally substituted on carbon with one or more R⁶;

X may be selected from -NH- and -O-;

R¹ in each occurrence may be independently selected from methyl, methoxy, isopropoxy and cyclopropyl;

R^2 may be selected from H and methyl;

R^3 may be selected from H and -CN;

R^5 may be methyl; and

R^6 may be fluoro.

In another aspect, **Ring A** may be selected from 5-methyl-1*H*-pyrazol-3-yl, 5-methoxy-1*H*-pyrazol-3-yl, 5-methyl-thiazol-2-yl, and 5-amino-2-cyano-1,3-thiazol-4-yl;

Ring B may be selected from 4-fluorophenyl, 5-fluoropyridin-2-yl, and 4-fluorophenylpyrimidin-2-yl;

X may be -NH-;

R^2 may be selected from H and methyl;

R^3 may be selected from H and -CN; and

R^5 may be methyl.

In yet another aspect, **Ring A** may be selected from 5-methyl-1*H*-pyrazol-3-yl, 5-methoxy-1*H*-pyrazol-3-yl, and 5-methyl-thiazol-2-yl;

Ring B may be selected from 4-fluorophenyl, 5-fluoropyridin-2-yl, and 4-fluorophenylpyrimidin-2-yl;

X may be -NH-;

R^2 may be selected from H and methyl;

R^3 may be selected from H and -CN; and

R^5 may be methyl.

In a further aspect, **Ring A** may be selected from 5-cyclopropyl-1*H*-pyrazol-3-yl, 5-isopropoxy-1*H*-pyrazol-3-yl, 5-methyl-1*H*-pyrazol-3-yl, 5-methoxy-1*H*-pyrazol-3-yl, and 5-methyl-thiazol-2-yl;

Ring B may be selected from 3,5-difluoropyridin-2-yl, 4-fluorophenyl, 5-fluoropyridin-2-yl, and 4-fluorophenylpyrimidin-2-yl;

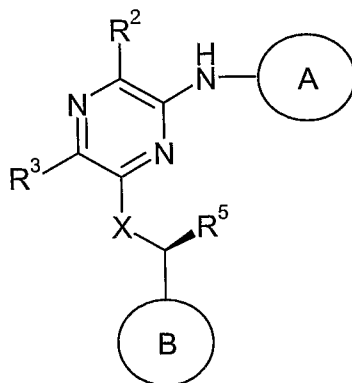
X may be selected from -NH- and -O-;

R^2 may be selected from H and methyl;

R^3 may be selected from H and -CN; and

R^5 may be methyl.

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



Formula (Ia)

or a pharmaceutically acceptable salt thereof, wherein **Ring A**, **Ring B**, R^2 , R^3 , X , and R^5 are as defined hereinabove.

In one aspect of the invention, 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), or a pharmaceutically acceptable salt thereof, selected from:

- N*-[(1*S*)-1-(5-Fluoropyrimidin-2-yl)ethyl]-*N'*-(5-methyl-1*H*-pyrazol-3-yl)pyrazine-2,6-diamine;
- N*-[(1*S*)-1-(5-Fluoropyrimidin-2-yl)ethyl]-*N'*-(5-methyl-1,3-thiazol-2-yl)pyrazine-2,6-diamine;
- N*-[(1*S*)-1-(5-Fluoropyridin-2-yl)ethyl]-*N'*-(5-methyl-1*H*-pyrazol-3-yl)pyrazine-2,6-diamine;
- N*-[(1*S*)-1-(5-Fluoropyridin-2-yl)ethyl]-*N'*-(5-methoxy-1*H*-pyrazol-3-yl)pyrazine-2,6-diamine;
- 3-{[(1*S*)-1-(5-Fluoropyrimidin-2-yl)ethyl]amino}-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile;
- 3-{[(1*S*)-1-(5-fluoropyridin-2-yl)ethyl]amino}-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile;
- 3-{[(1*S*)-1-(5-fluoropyrimidin-2-yl)ethyl]amino}-6-methyl-5-[(5-methyl-1*H*-pyrazol-3-

yl)amino]pyrazine-2-carbonitrile;
 3-{[(1*S*)-1-(5-fluoropyridin-2-yl)ethyl]amino}-6-methyl-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile;
N-[(1*S*)-1-(4-Fluorophenyl)ethyl]-*N'*-(5-methyl-1*H*-pyrazol-3-yl)pyrazine-2,6-diamine
 3-{[(1*S*)-1-(4-Fluorophenyl)ethyl]amino}-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile;
*N*⁶-[(1*S*)-1-(5-fluoropyridin-2-yl)ethyl]-3-methyl-*N*²-(5-methyl-1*H*-pyrazol-3-yl)pyrazine-2,6-diamine;
 3-{[(1*S*)-1-(5-fluoropyridin-2-yl)ethyl]amino}-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile;
 3-[(1*S*)-1-(5-fluoropyridin-2-yl)ethoxy]-6-methyl-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile;
 3-{[(1*S*)-1-(3,5-difluoropyridin-2-yl)ethyl]amino}-6-methyl-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile;
 3-{[(1*R*)-1-(3,5-Difluoropyridin-2-yl)ethyl]amino}-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile;
 3-{[(1*S*)-1-(5-fluoropyridin-2-yl)ethyl]amino}-6-methyl-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile;
 (S)-*N*²-(1-(5-Fluoropyridin-2-yl)ethyl)-*N*⁶-(5-isopropoxy-1*H*-pyrazol-3-yl)pyrazine-2,6-diamine;
 and
 (S)-5-(5-Cyclopropyl-1*H*-pyrazol-3-ylamino)-3-(1-(5-fluoropyridin-2-yl)ethylamino)pyrazine-2-carbonitrile.

Utility

JAK2

The compounds of Formula (I) 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 was 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 a 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.

Peptide substrate	TYK2 (Tyr 1054/1055 biotinylated peptide) Cell Signalling Technology #2200B. 402 μ M stock.
ATP Km	30 μ M
Assay conditions	150pM JAK2 enzyme, 30 μ M ATP, 80nM Tyk2, 10mM MgCl ₂ , 50mM Hepes buffer pH 7.5, 1mM DTT, 0.025%TWEEN 20.
Incubation	60 minutes, room temperature
Termination/Detection conditions	6.3mM HEPES, 30 mM EDTA, 525 μ g/ml BSA, 40 mM NaCl, 0.007%Triton® X-100, 12 ng/ml of Donor Beads, 12 ng/ml of Acceptor Beads
Detection incubation	overnight, room temperature
Fluometer settings	Excitation = 680 nm Emission = 570 nm Excitation Time = 180 ms Total Measurement Time=550 ms

Although the pharmacological properties of the compounds of the Formula (I) vary with structural change, in general the compounds of the Formula (I) are believed to demonstrate activity at IC₅₀ concentrations (concentrations to achieve 50% inhibition) or doses at a level below 10 μ M.

When tested in the above in-vitro assay the JAK inhibitory activity of the following example was measured at the following IC₅₀.

Ex	IC ₅₀ (μ M)
9	0.003

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 3 μ M, providing the indicated JAK inhibitory %. In those instances where the compound was tested more than once, 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.

Table 1

Example	Inhibition (%) at 3 μ M
1	100
2	100
3	100
4	100
5	100
6	100
7(a)	100
7(b)	98
8(a)	100
8(b)	100
9	100
10	100
11	100
12	99
13(a)	99
13(b)	97
14	99
15	99
16	100
17	100

TRK

The compounds of Formula (I) have utility for the treatment of cancer by inhibiting the TRK tyrosine kinases, particularly the Trk A and B families. Methods of treatment target tyrosine

kinase activity, particularly the Trk activity and more particularly Trk A and B activity, which is involved in a variety of cancer related processes. Thus, inhibitors of tyrosine kinase, particularly the Trks and more particularly Trk A and B, are expected to be active against neoplastic disease such as carcinoma of the breast, ovary, lung, colon, prostate or other tissues, as well as leukemias 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 Trk inhibitors and more particularly Trk A and B inhibitors are also expected to be useful for the treatment other proliferative diseases including but not limited to autoimmune, inflammatory, neurological, and cardiovascular diseases.

In addition, the compounds of the invention are expected to be of value in the treatment or prophylaxis of cancers selected with up regulated or constitutively activated Trk kinases, including but not limited to, oncogenic rearrangements leading to ETV6-TrkC fusions, TRP-TrkA fusions proteins, AML-ETO (t8;21), autocrine or paracrine signalling leading to elevated serum levels of NGF, BDNF, neurotrophins or tumors with constitutively active Trk associated with disease aggressiveness, tumor growth and proliferation or survival signalling.

Compounds of the present invention have been shown to inhibit tyrosine kinases, particularly the Trks and more particularly Trk A and B, as determined by the Trk A Assay described herein.

Compounds provided by this invention should also be useful as standards and reagents in determining the ability of a potential pharmaceutical to inhibit tyrosine kinases, particularly the Trks and more particularly Trk A and B. These would be provided in commercial kits comprising a compound of this invention.

Trk A kinase activity was 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 Trk A kinase activity, the intracellular domain of a HIS-tagged human Trk A kinase (amino acids 442-796 of Trk A, Swiss-Prot Primary Accession Number P04629) was expressed in SF9 cells and purified using standard nickel column chromatography. After incubation of the kinase with a biotinylated substrate and adenosine triphosphate (ATP) for 20 minutes at room temperature, the kinase reaction was stopped by the addition of 30 mM ethylenediaminetetraacetic acid (EDTA). The reaction was performed in 384 well microtitre plates and the reaction products were 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.

Peptide substrate	PolyEY-biotin (PGT-bio.)
ATP Km	70 μ M
Assay conditions	0.838 ng/ml Trk A, 9 mM HEPES, 45 μ g/ml BSA, 10 mM MnCl ₂ , 5 nM PGT-bio, 0.01% Triton® X-100, 70 μ M ATP
Incubation	20 minutes, room temperature
Termination/Detection conditions	6.3mM HEPES, 30 mM EDTA, 525 μ g/ml BSA, 40 mM NaCl, 0.007%Triton® X-100, 12 ng/ml of Donor Beads, 12 ng/ml of Acceptor Beads
Detection incubation	overnight, room temperature
Fluometer settings	Excitation = 680 nm Emission = 570 nm Excitation Time = 180 ms Total Measurement Time=550 ms

Although the pharmacological properties of the compounds of the Formula (I) vary with structural change, in general activity possessed by compounds of the Formula (I) may be demonstrated at IC₅₀ concentrations (concentrations to achieve 50% inhibition) or doses at a level below 10 μ M.

When tested in the above in-vitro assay the Trk inhibitory activity of the following example was measured at the following IC₅₀s.

Ex	IC ₅₀ (μM)
10	0.670

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 use in 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 use in 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 use in 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 use in 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 use in the production of a JAK inhibitory effect.

In yet a further 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 use in the production of a TRK inhibitory effect.

In one 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 use in the treatment of cancer.

In another 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 still 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 yet another aspect, there is provided a method 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, said method comprising administering to said animal an effective amount of compound of Formula (I), or a pharmaceutically acceptable salt thereof.

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

In one aspect, where reference is made to the Trk inhibitory effect, this may particularly refer to a Trk A inhibitory effect.

In another aspect, where reference is made to the Trk inhibitory effect, this may particularly refer to a Trk B inhibitory effect.

In still another 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, 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 still another 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 yet another 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 *p*-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

polyoxyethylene 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 *p*-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); antimetabolites (for example antifolates such as fluoropyrimidines such as 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 proteasome 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, droloxifene and idoxifene), 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 5 α -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-erbB2 antibody trastuzumab [Herceptin™] and the anti-erbB1 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, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)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 phosphatidylinositol 3-kinase (PI3K) and for example inhibitors of mitogen activated protein kinase kinase (MEK1/2) and for example inhibitors of protein kinase B (PKB/Akt), for example inhibitors of Src tyrosine kinase family and/or Abelson (Abl) tyrosine kinase family such as AZD0530 and dasatinib (BMS-354825) and imatinib mesylate (Gleevec™); 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 $\alpha v \beta 3$ function and angiostatin);
 - (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 [Revlimid®]; and
- (x) 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, the compound of Formulas (I) and its pharmaceutically acceptable salts 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**).

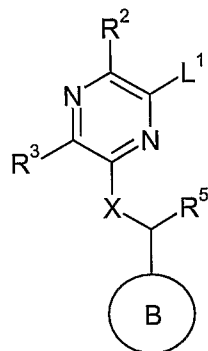
Compounds of Formula (I) may be prepared in a variety of ways. The Processes and Schemes shown below illustrate some methods for synthesizing compounds of Formula (I) and intermediates which may be used for the synthesis of compounds of Formula (I) (wherein Ring A, Ring B, X, R², R³, and R⁵, unless otherwise 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 and Schemes 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 and Schemes.

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 Schemes herein, to obtain necessary starting materials and products.

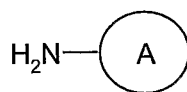
In one aspect, compounds of Formula (I) may be prepared by:

1) Process A - reacting a pyrazine of Formula (A):



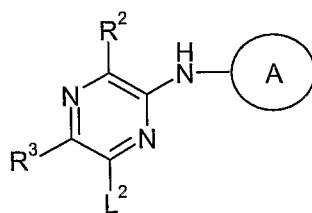
Formula (A)

with an amine of Formula (B):



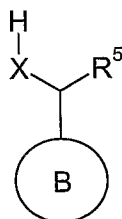
Formula (B) ; or

2) Process B - reacting a pyrazine of Formula (C):



Formula (C)

with a compound of Formula (D):



Formula (D);

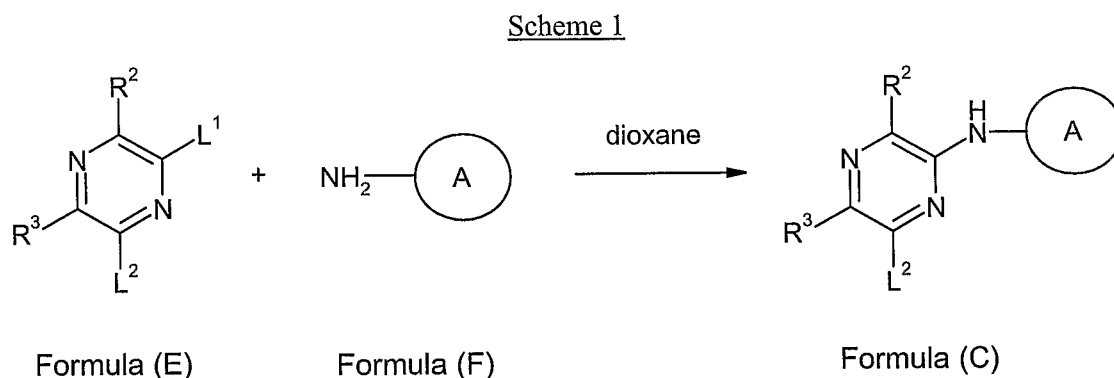
and thereafter if appropriate:

- 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^1 and L^2 are leaving groups.

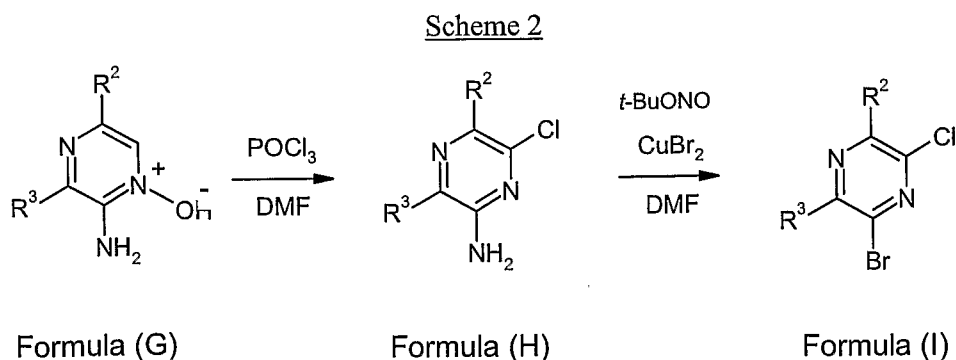
More particularly, with regard to Process A, the pyrazine of Formula (A) and the amine of Formula (B) may be reacted together in the presence of a suitable solvent, examples of which include ketones such as acetone, alcohols such as ethanol and butanol, and aromatic hydrocarbons such as toluene and N-methyl pyrrolid-2-one. Such reaction may advantageously occur in the presence of a suitable base, examples of which include inorganic bases such as cesium carbonate and potassium carbonate, and organic bases such as triethylamine and diisopropyl ethyl amine (DIPEA). The reaction is advantageously performed at a temperature in a range from 0°C to reflux.

In another aspect, pyrazine of Formula (A) and the amine of Formula (B) may be reacted together under standard Buchwald conditions (for example see *J. Am. Chem. Soc.*, **118**, 7215; *J. Am. Chem. Soc.*, **119**, 8451; *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 *t*-butoxide. Such a reaction may be advantageously occur in the presence of palladium acetate. Solvents suitable for such a reaction include aromatic solvents such as toluene, benzene, or xylene.

The pyrazine of Formula (C) may be prepared according to **Scheme 1**:



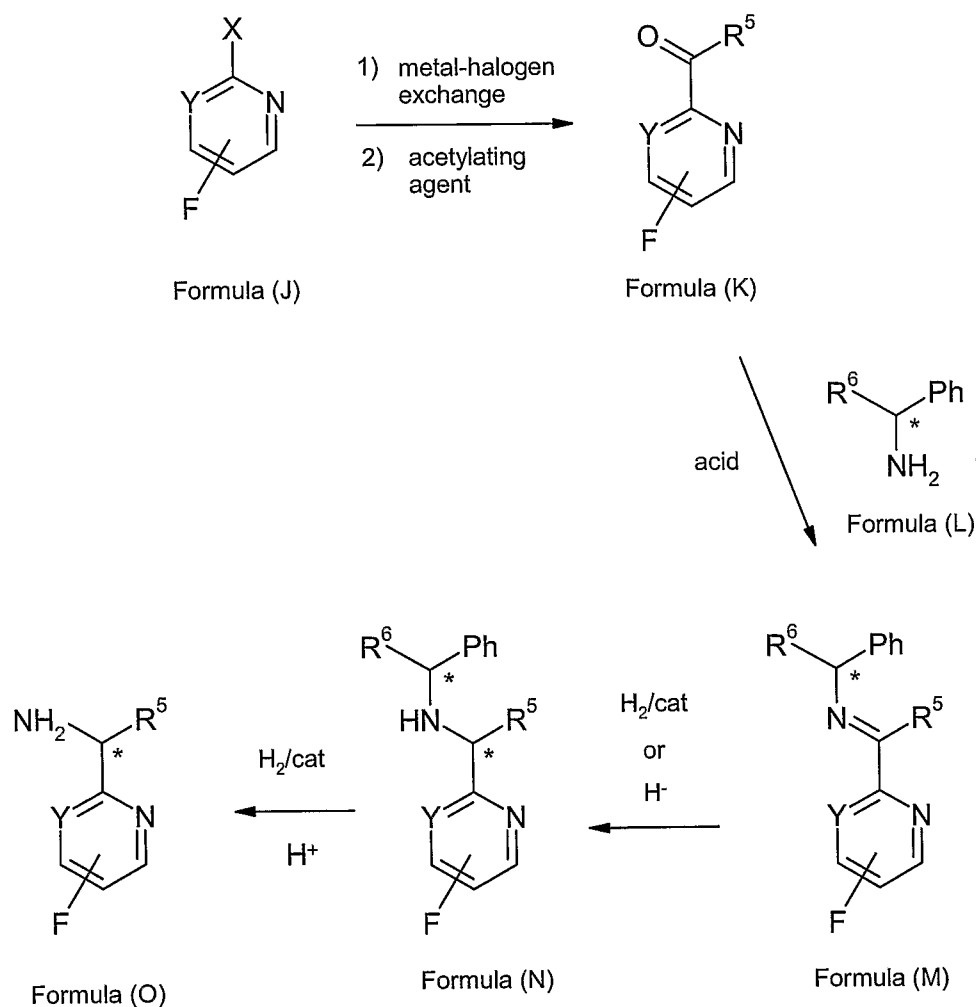
The skilled chemist will be able to choose the substituents and leaving groups of the pyrazine of Formula (E) so as to effect replacement of the desired leaving group by aminon group on the compound of Formula (F). For example, in some instances it may be advantageous for the chemist to choose a different leaving group for L^1 than is used for L^2 .



Pyrazines of Formula (E) are commercially available compounds, known in the literature, and/or may be prepared by standard processes known in the art. **Scheme 2** depicts a typical process that may be used for the synthesis of a pyrazine of Formula (E) containing different leaving groups L^1 and L^2 , L^1 being chloro and L^2 being bromo (depicted by Formula (I)). The pyrazine oxide of Formula (G) may be prepared according to procedures analogous to those described for the syntheses of Intermediates 19 and 23. The pyrazine oxide may be reacted with a suitable chlorinating agent to provide the pyrazine of Formula (H). Reaction of the pyrazine of Formula (H) with a suitable brominating agent replaces the amino substituent with a bromo substituent, providing the pyrazine of Formula (I).

Compounds of Formula (O), which are compounds of Formula (D) in which **Ring B** is pyrimidinyl or pyridinyl, and bears a fluoro substituent, in which R^5 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R^{50} (wherein R^{50} is as described hereinabove), and in which R^6 is selected from -CN, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, heterocyclyl, may be prepared according to the procedure depicted in **Scheme 3**. The asterisk shown in the compounds of Formulas (J) through (O) is intended to indicate a particular stereochemical configuration.

Scheme 3

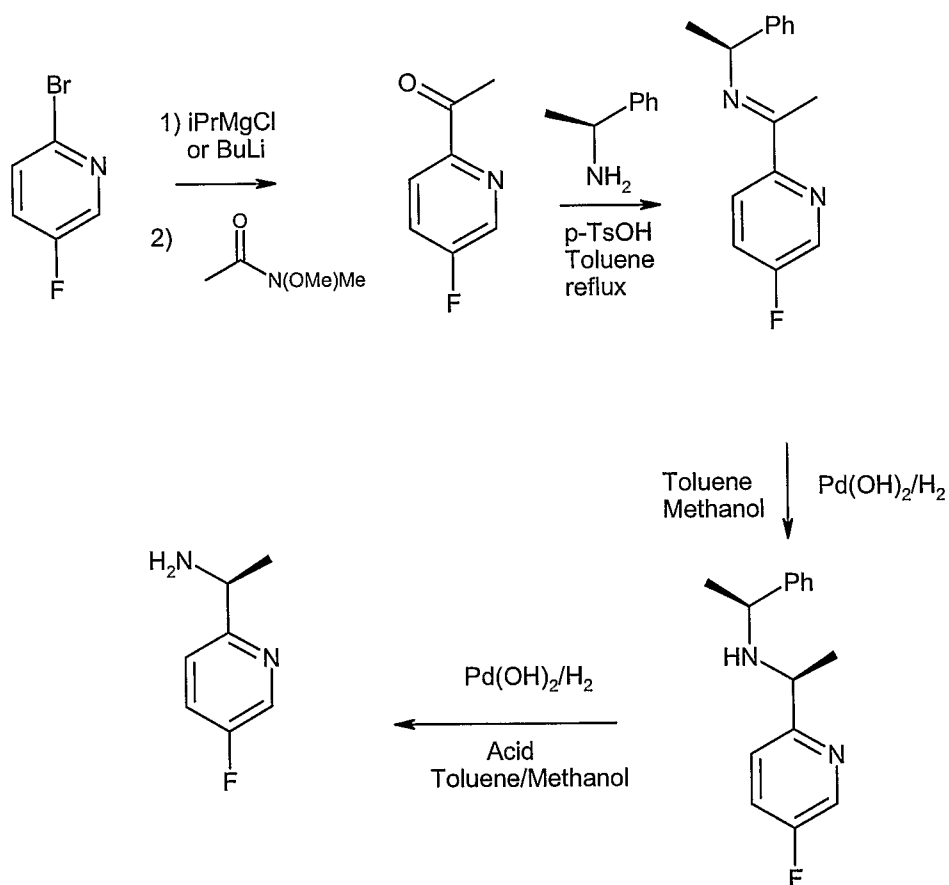


A compound of Formula (K) may be obtained by subjecting a compound of Formula (J) (in which X is halo) to metal-halogen exchange conditions, followed by treatment with a suitable acetylating reagent. The metal-halogen exchange may be effected under typical Grignard conditions, or using alkyl lithiums. The acetylating reagent can be any electrophilic acetyl type compound, such as dimethylacetamide. Reaction of the compound of Formula (K) with a compound of Formula (L) in the presence of a suitable acid results in a compound of Formula (M). A compound of Formula (M) may be converted to a compound of Formula (N) via hydrogenation with a suitable catalyst such as Pd(OH)₂. While such reaction conditions do promote the conversion of a compound of Formula (M) to a compound of Formula (O), the

addition of acids such as tartaric acid, acetic acid, and citric acid advantageously drives the reaction to completion. Catalysts suitable for promoting the transformation of a compound of Formula (N) to a compound of Formula (O) include metal catalysts obtained from metals such as palladium, platinum, and nickel.

A specific example of the process of **Scheme 3** is shown below in **Scheme 3(a)**, which depicts the preparation of (S)-1-(5-Fluoro-pyridin-2-yl)-ethylamine:

Scheme 3(a)



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 other wise stated; evaporation of organic solvent was 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 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) 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;
- (vii) 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;
- (viii) chemical symbols have their usual meanings;
- (ix) solvent ratio was given in volume : volume (v/v) terms.
- (x) "ISCO" refers to normal phase flash column chromatography using pre-packed silica gel cartridges (12 g, 40 g etc.), used according to the manufacturer's instructions, obtained from ISCO, Inc, 4700 Superior Street Lincoln, NE, USA.
- (xi) A "Gilson column" refers to a YMC-AQC18 reverse phase HPLC Column with dimension 20 mm/100 and 50 mm/250 in H₂O/MeCN with 0.1% TFA as mobile phase unless otherwise stated and used according to the manufacturer's instructions, obtained from Gilson, Inc. 3000 Parmenter Street, Middleton, WI 53562-0027, U.S.A.
- (xii) "Biotage column" refers to normal phase flash column chromatography using pre-packed silica gel cartridges (12g, 40g, 80 g etc.), used according to the manufacturer's

- instructions, obtained from Biotage Inc, 1725 Discovery Drive Charlottesville, Virginia 22911, USA.
- (xiii) "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) and used according to the manufacturers instruction obtained from SFC Mettler Toledo AutoChem, Inc. 7075 Samuel Morse Drive Columbia MD 21046, U.S.A.
- (xiv) Chiralcel OJ[®] and Chiralcel AD-H[®] or Chiralpak[®] columns are used according to the manufacturers instruction obtained from Chiral Technologies, Inc. 800NorthFivePointsRoad WestChester, PA19380, USA.
- (xv) 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.
- (xvi) The following abbreviations have been used:
- | | |
|------------------------------------|---|
| Boc ₂ O | di- <i>tert</i> -butyl-dicarbonate |
| DCM | dichloromethane |
| DIPEA | N, N-diisopropylethylamine |
| DMF | <i>N,N</i> -dimethylformamide |
| DMAP | 4-dimethylaminopyridine |
| DMSO | dimethylsulfoxide |
| dppf | 1,1'-Bis(diphenylphosphino)ferrocene |
| EtOAc | ethyl acetate |
| Et ₂ O | diethyl ether |
| GC | gas chromatography |
| GC-MS | gas chromatography-mass spectroscopy |
| HPLC | high-performance liquid chromatography |
| LCMS | liquid chromatography/mass spectroscopy |
| Pd ₂ (dba) ₃ | Tris(dibenzylideneacetone)dipalladium (0) |
| THF | tetrahydrofuran |
| Xantphos | 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene |

Intermediate 1**5-Fluoropyrimidine-2-carbonitrile**

A 10 ml microwave vial was charged with 2-chloro-5-fluoropyrimidine (2.0 g, 15.09 mmol), Pd₂(dba)₃ (0.549 g, 0.6 mmol), dppf (0.67 g, 1.21 mmol), zinc cyanide (1.15 g, 9.81 mmol), and zinc dust (0.237 mg, 3.62 mmol). The flask was evacuated and backfilled with N₂, and anhydrous dimethylacetamide. The vial was mounted onto a Personal Chemistry microwave reactor and heated at 100 °C for 10 hours. The reaction mixture was diluted with EtOAc and then washed with brine three times. The organic layer was obtained and evaporated to dryness. The dried residue was purified by silica gel chromatography (By ISCO Combiflash with gradient EtOAc and hexanes), providing the title compound as a creamy solid (1.50 g, 80%).

GC-MS: 123 (M).

¹H NMR (CDCl₃) δ: 8.80 (s, 2H).

Intermediate 2**N-(1-(5-Fluoropyrimidin-2-yl)vinyl)acetamide**

5-Fluoropyrimidine-2-carbonitrile (**Intermediate 1**, 1.0 g, 8.1 mmol) in THF (10 ml) was added a solution of MeMgBr (3.3 ml, 9.75 mmol) in ether dropwise at 0 °C. After addition, the reaction mixture was warmed to room temperature, stirred at room temperature for 1 hour and then diluted with DCM (10 ml). Acetic anhydride (1.23 ml, 13.0 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 1 hour and 40 °C for 1 hour. Saturated sodium bicarbonate solution (10 ml) was added and an extraction was carried out with EtOAc (2x20 ml). The combined organic layers were dried over sodium sulfate. After removal of solvent, the resulting residue was purified by column chromatography (hexane:EtOAc = 2.5 : 1) to give the title compound as a white solid (0.38 g, 26%).

LCMS: [M+H]⁺ 182.

¹H NMR (400 MHz) δ: 9.34 (s, 1H), 8.95 (s, 2H), 6.25 (s, 1H), 6.03 (s, 1H), 2.11 (s, 3H).

Intermediate 3**N-[(1S)-1-(5-Fluoropyrimidin-2-yl)ethyl]acetamide**

N-(1-(5-Fluoropyrimidin-2-yl)vinyl)acetamide (**Intermediate 2**, 0.10 g, 0.55 mmol) in MeOH (5 ml) under N₂ was added (+)-1,2-bis((2S, 5S)-2,5-diethylphospholano)benzene

(cyclooctadiene)rhodium(I)trifluoromethanesulfonate (0.04 g, 0.0055 mmol). The solution was transferred to a high pressure bomb and charged with 150 psi H₂. The reaction mixture was stirred at room temperature for 4 hours. The solvent was removed and the resulting residue was purified by column chromatography (EtOAc) to give the title compound as a white solid (0.096 g, 95%).

LCMS: [M+H]⁺ 184.

¹H NMR (400 MHz) δ : 8.84 (d, J = 0.8 Hz, 2H), 8.34 (d, J = 7.6 Hz, 1H), 5.00 (m, 1H), 1.84 (s, 3H), 1.37 (d, J = 6.8 Hz, 3H).

Enantiomeric excess determined by HPLC (Chiralpak IA; 95:5 CO₂/MeOH), >99% ee.

Intermediate 4

tert-Butyl [(1*S*)-1-(5-fluoropyrimidin-2-yl)ethyl]carbamate

N-[(1*S*)-1-(5-Fluoropyrimidin-2-yl)ethyl]acetamide (**Intermediate 3**, 0.20 g, 1.09 mmol), DMAP (0.027 g, 0.22 mmol) and di-*tert*-butyl-dicarbonate (0.60 g, 2.73 mmol) in THF (10 ml) was stirred at 50 °C for 40 hours. After cooling to room temperature, lithium hydroxide monohydrate (0.094 g, 2.24 mmol) and water (10 ml) was added. The reaction mixture was stirred at room temperature for 9 hours. Ether (30 ml) was added, organic layer was separated, washed with brine (20 ml) and dried over sodium sulfate. After removal of solvent, the resulting residue was purified by column chromatography (Hex-EtOAc=5:1) to give the title compound as a pale yellow oil (0.21 g, 80%).

LCMS: [M+H]⁺ 242.

¹H NMR (400 MHz) δ : 8.84 (s, 2H), 7.24 (d, J = 7.6 Hz, 1H), 4.74 (m, 1H), 1.35 (s, 12H).

Intermediate 5 (Synthetic Route A)

(1*S*)-1-(5-Fluoropyrimidin-2-yl)ethanamine hydrochloride

To a solution of *tert*-butyl [(1*S*)-1-(5-fluoropyrimidin-2-yl)ethyl]carbamate (**Intermediate 4**, 0.21 g, 0.87 mmol) in DCM (5 ml) was added HCl (1.3 ml, 5.2 mmol) in dioxane. The reaction mixture was stirred at room temperature for 3 hours. The solvent was removed to give the title compound as white solid (quantitative).

LCMS: [M+H]⁺ 142.

Intermediate 5 was also prepared from 5-fluoropyrimidine-2-carbonitrile (**Intermediate 1**) via **Intermediates 6, 7, and 8**, using the following alternative synthetic route, Synthetic Route B.

Intermediate 6

5-Fluoropyrimidine-2-carbaldehyde

To a solution of 5-fluoropyrimidine-2-carbonitrile (**Intermediate 1**, 1.0 g, 8.1 mmol) in anhydrous THF at -78°C was added a solution of DIBAL-H (8.1 mL) over a period of 20 minutes. The resulting mixture was stirred at this temperature for 2 hours whereupon MeOH was added. The solution was allowed to warm to room temperature whereupon a solution of concentrated HCl was added. The resulting mixture was stirred for 2 hours at ambient temperature and the aqueous layer was washed with EtOAc (3x). The combined organic extracts were washed with brine and dried (MgSO_4). Evaporation of the solvent afforded the titled compound (780 mg, 76%).

LCMS: $[\text{M}+\text{H}]^+$ 127.

Intermediate 7

***N*-[(1*Z* and/or *E*)-(5-Fluoropyrimidin-2-yl)methylene]-2-(*R*)-methylpropane-2-sulfinamide**

To a solution of 5-fluoropyrimidine-2-carbaldehyde (**Intermediate 6**, 1.55 g, 12.3 mmol) in anhydrous DCM at room temperature were added 2-(*R*)-methylpropane-2-sulfinamide (1.79 g, 14.7 mmol) and anhydrous copper(II)sulfate (1.96 g, 12.28 mmol). The resulting mixture was stirred at this temperature for 24 hours, the solid was filtered under vacuum, washed with DCM (3x) and evaporation of the solvents afforded a yellow oil. The resulting residue was purified by column chromatography (Hex-EtOAc=3:1), providing the title compound (1.94 g, 69%).

LCMS: $[\text{M}+\text{H}]^+$ 232.

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ : 9.13 (s, 2 H) 8.47 (s, 1 H) 0.99 (s, 9 H).

Intermediate 8

***N*-[(1*S*)-1-(5-Fluoropyrimidin-2-yl)ethyl]-2-(*R*)-methylpropane-2-sulfinamide**

To a solution of *N*-[(1*Z* and/or *E*)-(5-fluoropyrimidin-2-yl)methylene]-2-(*R*)-methylpropane-2-sulfinamide (**Intermediate 7**, 1.94 g, 8.5 mmol) in anhydrous THF at -20°C was added slowly a solution of MeMgBr (9.3 mL, 9.3 mmol). The resulting mixture was stirred at this temperature

for 3 hours whereupon it partitioned between H₂O and EtOAc. The aqueous layer was extracted with EtOAc (3x) washed with brine, dried (MgSO₄). Evaporation of the solvents under reduced pressure under vacuum afforded yellow oil. The resulting residue was purified by column chromatography (100% EtOAc), providing the title compound (660 mg, 50%).

LCMS: [M+H]⁺ 246

¹H NMR (300 MHz, DMSO-d₆) δ 8.89 (s, 2 H) 5.53 (d, 1 H) 4.43 - 4.65 (m, 1 H) 1.46 (d, 3 H) 1.11 (s, 9 H).

Intermediate 5 (Synthetic Route B)

(1S)-1-(5-Fluoropyrimidin-2-yl)ethanamine hydrochloride

To a solution of *N*-[(1S)-1-(5-fluoropyrimidin-2-yl)ethyl]-(2R)-methylpropane-2-sulfinamide (**Intermediate 8**, 655 mg, 2.67 mmol) in dry dioxane (20 ml) was added HCl (3.4 ml, 13.3 mmol) in dioxane. The reaction mixture was stirred at room temperature for 3 hours. The solvent was removed, providing the title compound as white solid.

LCMS: [M+H]⁺ 142.

Intermediate 9

6-Chloro-*N*-[(1S)-1-(5-fluoropyrimidin-2-yl)ethyl]pyrazin-2-amine

(1S)-1-(5-Fluoropyrimidin-2-yl)ethanamine hydrochloride (**Intermediate 5**) and 2,6-dichloropyrazine were reacted using a procedure similar to the one described for the synthesis of **Intermediate 27**, providing the title compound.

LCMS: [M+H]⁺ 254

Intermediate 10

***tert*-Butyl 3-amino-5-methyl-1*H*-pyrazole-1-carboxylate**

5-Methyl-1*H*-pyrazol-3-amine and Boc₂O were reacted using a procedure similar to the one described for the synthesis of **Intermediate 18**, providing the title compound.

LCMS: [M+H]⁺: 198

Intermediate 11**5-Fluoropyridine-2-carbonitrile**

2-Bromo-5-fluoropyridine (93.0 g, 528 mmol), Zn dust (8.29 g, 127 mmol), zinc cyanide (40.3 g, 343 mmol), 1,1'-bis(diphenylphosphino)ferrocene (11.7 g, 21.1 mmol) and Pd₂dba₃ (9.68 g, 10.6 mmol) in anhydrous DMA (300 ml) were heated at 95 °C for 3 hours. After cooling to room temperature, brine (100 ml) and ether (500 ml) was added. The solid formed was removed by filtration and washed with ether (300 ml). The organic layer was separated, washed with brine (200 ml) and dried over sodium sulfate, and concentrated. After removal of solvent, the resulting residue was purified by column chromatography (hexane:DCM = 1:1), providing the title compound as a white solid (49 g, 72%).

¹H NMR (400 MHz) δ: 8.82 (d, 1H), 8.21 (dd, 1H), 8.05 (dd, 1H).

Intermediate 12**N-(1-(5-Fluoropyridin-2-yl)vinyl)acetamide**

A solution of MeMgBr (170.3 ml, 510.98 mmol) in ether was diluted with 170 ml of anhydrous THF and cooled to 0 °C. 5-Fluoropyridine-2-carbonitrile (**Intermediate 11**, 53.6 g, 425.82 mmol) in THF (170 ml) was added dropwise. The reaction mixture was stirred at 0 °C for 30 minutes, then diluted with DCM (170 ml). Acetic anhydride (48.3 ml, 510.98 mmol) in DCM (100 ml) was added dropwise at 0 °C. After the addition, the reaction mixture was warmed to room temperature and stirred at room temperature for 8 hours. Saturated sodium bicarbonate solution (50 ml) was added and an extraction was carried out with EtOAc (2 x 200 ml). The combined organic layers were dried over sodium sulfate. After removal of solvent, the resulting residue was purified by column chromatography (hexane:EtOAc = 2.5 : 1), providing the title compound as a white solid (26.6 g, 35%).

LCMS: [M+H]⁺ 181.

¹H NMR (400 MHz) δ: 9.37 (s, 1H), 8.57 (d, *J* = 2.8 Hz, 1H), 7.81 (m, 2H), 6.01 (s, 1H), 5.52 (s, 1H), 2.08 (s, 3H).

Intermediate 13***N*-[*(1S)*-1-(5-Fluoropyridin-2-yl)ethyl]acetamide**

To a solution of *N*-(1-(5-fluoropyridin-2-yl)vinyl)acetamide (**Intermediate 12**, 11.0 g, 61.1 mmol) in MeOH (120 ml) under N₂ was added (+)-1,2-bis((2*S*, 5*S*)-2,5-diethylphospholano) benzene (cyclooctadiene)rhodium(I)trifluoromethanesulfonate (0.441 g, 0.611 mmol). The solution was transferred to a high pressure bomb and charged 150 psi H₂. The reaction stirred at room temperature and maintained inside pressure between 120-150 psi for 7 hours. The solvent was removed and the resulting residue was purified by column chromatography (EtOAc), providing the title compound as a white solid (9.8 g, 88%).

LCMS: [M+H]⁺ 183.

¹H NMR (400 MHz) δ : 8.49 (d, J = 2.4 Hz, 1H), 8.32 (d, J = 7.6 Hz, 1H), 7.66 (m, 1H), 7.39 (dd, J = 4.4 and 8.8 Hz, 1H), 4.95 (m, 1H), 1.85 (s, 3H), 1.34 (d, J = 7.2 Hz, 3H). Enantiomeric excess determined by HPLC (Chiralpak IA; 70:30 CO₂/MeOH), 95.3% ee.

Intermediate 14***tert*-Butyl [(1*S*)-1-(5-fluoropyridin-2-yl)ethyl]carbamate**

A solution of *N*-[*(1S)*-1-(5-fluoropyridin-2-yl)ethyl]acetamide (**Intermediate 13**, 11.0 g, 60.37 mmol), DMAP (1.48 g, 12.07 mmol) and di-*tert*-butyl-dicarbonate (26.35 g, 120.7 mmol) in THF (100 ml) was stirred at 50 °C for 20 hours. After cooling to room temperature, lithium hydroxide monohydrate (5.19 g, 123.8 mmol) and water (100 ml) were added. The reaction mixture was stirred at room temperature for 5 hours and diluted with ether (200 ml). The organic layer was separated, washed with brine (100 ml), and dried over sodium sulfate. After removal of solvent, the resulting residue was purified by column chromatography (hexane:EtOAc = 5 : 1), providing the title compound as a pale yellow oil (13.6 g, 94%).

LCMS: [M+H]⁺ 241.

¹H NMR (400 MHz) δ : 8.46 (d, J = 2.8 Hz, 1H), 7.69 (m, 1H), 7.35-7.41 (m, 2H), 4.67 (m, 1H), 1.37 (s, 9H), 1.32 (d, J = 7.2 Hz, 3H).

Intermediate 15**[(1*S*)-1-(5-Fluoropyridin-2-yl)ethyl]amine**

To a solution of *tert*-butyl [(1*S*)-1-(5-fluoropyridin-2-yl)ethyl]carbamate (**Intermediate 14**, 12.8 g, 53.3 mmol) in DCM (100 ml) was added HCl/dioxane solution (107 ml, 4N, 428 mmol). The reaction mixture was stirred at room temperature for 3 hours. The solvent was removed and 50 ml of saturated sodium bicarbonate was added. The resulting aqueous solution was extracted with ether (6 x 400 ml), dried over sodium sulfate and concentrated to give the title compound (7.30 g, 98%) as pale yellow oil.

LCMS: $[M+H]^+$ 141.

^1H NMR (400 MHz) δ : 8.44 (d, 1H), 7.66 (m, 1H), 7.53 (m, 1H), 4.01 (q, 1H), 1.94 (b, 2H), 1.26 (d, 3H).

Intermediate 16**6-Chloro-*N*-[(1*S*)-1-(5-fluoropyridin-2-yl)ethyl]pyrazin-2-amine**

[(1*S*)-1-(5-Fluoropyridin-2-yl)ethyl]amine (**Intermediate 15**) and 2,6-dichloropyrazine were reacted using a procedure similar to the one described for the synthesis of **Intermediate 27**, providing the title compound. LCMS: $[M+H]^+$ 253

Intermediate 17**5-Methoxy-1*H*-pyrazol-3-amine**

To a solution of 3-amino-5-hydroxypyrazole (50.00 g) in CH_2Cl_2 (800 mL) was added triphenylphosphine (155.64 g) and the resulting mixture was cooled to 0°C. Diisopropyl azodicarboxylate (117.64 mL) was added drop-wise over a period of 35 minutes (temp < 2°C) to give a dark brown, mobile slurry. The reaction mixture was then maintained at 0°C for 1 hr. A beige precipitate came out of solution after 20 minutes. Methyl Alcohol (50 mL) was then added drop-wise over a period of 15 minutes at 0°C as the slurry thinned considerably to give a lighter yellow slurry. The reaction mixture was then held at 0°C for 1 hour. The reaction mixture was warmed slowly to ambient temperature over a period of 2 hours. The reaction mixture was then held at ambient temp for 22 hours. The reaction mixture was filtered to remove undissolved solids. The filtrate was dried (MgSO_4) and concentrated under reduced pressure to give a yellow-

orange oil. Purification by column chromatography (5%→10% MeOH/CH₂Cl₂) provided the title compound as a waxy solid.

LCMS: [M+H]⁺ 114.

¹H NMR (300 MHz, DMSO-d₆) δ: 4.67 (s, 1 H) 3.61 (s, 3 H).

The hydrochloride salt of the title compound may be prepared according to the procedure described below:

To a stirred solution of malononitrile (1.00 eq) and methanol (1.00 eq) in Et₂O (5.1 v/w) at 15°C, under nitrogen, was added Et₂O/HCl (1M, 1.00 eq) over 35 minutes, maintaining an internal temperature of 10 - 15°C. Upon completion of the addition, the reaction mixture was heated to, and stirred at, 25°C for 16 hours. The resultant suspension was cooled to 20 °C and filtered, and the collected solid was washed with Et₂O (3 x 1 bed vol.) and dried *in vacuo* at ~40°C for 7 hours, to afford methyl 2-cyanoethanimidate hydrochloride as a pale cream solid.

A suspension of methyl 2-cyanoethanimidate hydrochloride (1 eq) in methanol (10 v/w) over CaCl₂ was stirred at ambient temperature overnight. The resultant solution was concentrated *in vacuo* and the residue dissolved in EtOAc (6.67 v/w), washed with 10% aq. Na₂CO₃ (3.33 v/w) and brine (3.33 v/w). The separated organic phase was dried over MgSO₄, filtered and concentrated *in vacuo* to afford 3,3,3-trimethoxy propanenitrile in good purity as a brown oil. To a solution of 3,3,3-trimethoxy propanenitrile (1 eq.) in MeOH (10 v/w) was added hydrazine monohydrochloride (1.02 eq.). Upon completion of the addition, the reaction mixture was heated to, and stirred at, reflux (ca. 67°C) for 6 hours. The batch was allowed to cool overnight and then concentrated *in vacuo* to afford the crude hydrochloride product as a sticky brown solid. Purification was accomplished by dissolution in MTBE/MeOH (9:1, 5 v/w on crude product) at ~50°C for 30 minutes and then cooling to 20°C. The suspension was filtered, washed with MTBE (3 x 1 bed vol.) and dried *in vacuo* at 50°C to give the title product in excellent purity as its hydrochloride salt.

Intermediate 18**tert-Butyl 3-amino-5-methoxy-1H-pyrazole-1-carboxylate**

To a solution of 5-methoxy-1H-pyrazol-3-amine (**Intermediate 17**, 2.48 g, 17.6 mmol) in CH₂Cl₂ (70 mL) was added Boc₂O (4.0 g, 18.5 mmol) followed by a 4.5 M solution of KOH (31 mL, 140.8 mmol) at 0°C. The resulting mixture was stirred at ambient temperature overnight, diluted with more CH₂Cl₂. The combined organic layers dried (MgSO₄) and evaporated to give a yellow oil. Purification by column chromatography (Biotage column, 20% to 30% EtOAc/hexanes) provided the title compound as solid.

LCMS: [M+H]⁺ 214

Intermediate 19**2-Amino-3-cyano-1N-pyrazine oxide**

To a solution of glycol (15 ml, 30% w/v in H₂O) and acetone oxime (5.0 g) in H₂O (20 mL) was added aminomalononitrile *p*-toluenesulfonate (16.41 g) and the resulting mixture was stirred overnight at room temperature. The title compound started to precipitate after 10 minutes of complete dissolution of the aminomalonitrile *p*-toluenesulfonate had occurred, and was collected by filtration the next day as the *p*-toluenesulfonate salt.

LCMS: [M+H]⁺ 169.

¹H NMR (300 MHz, DMSO-d₆) δ 8.72 (d, 1 H) 8.49 (d, 2 H), 8.00 (br.s, 1 H) 7.86 (d, 2 H), 7.55 (s, 1 H) 2.56 (s, 3 H).

Intermediate 20**3-Amino-5-chloropyrazine-2-carbonitrile**

To a solution of 2-amino-3-cyano-1N-pyrazine oxide (**Intermediate 19**, 1.5 g) in DMF (15 ml) was added POCl₃ (3ml), at 0°C, at such a rate that the internal temperature did not exceed 5°C. The resulting dark solution was heated to 80°C for 1 hr. The solution was cooled to room temperature and was poured with caution into ice with vigorous stirring. The resulting suspension was stirred overnight at room temperature. The title compound was isolated by filtration.

¹H NMR (300 MHz, DMSO-d₆) δ 7.96 (s, 1 H) 7.81 (br.s, 2 H).

Intermediate 21**3-Bromo-5-chloropyrazine-2-carbonitrile**

A solution of 3-amino-5-chloropyrazine-2-carbonitrile (**Intermediate 20**, 1.02 g, 6.6 mmol) in DMF (10 ml) was added drop-wise to a solution of CuBr₂ (1.63 g, 7.28 mmol) and t-BuONO (2.79 g, 33.1 mmol) in DMF at 65°C. The resulting mixture was heated at this temperature for 30 minutes and then poured into ice-water. The aqueous layer was extracted with EtOAc and combined organic layers were dried (Na₂SO₄) and evaporated, providing a solid. Purification by column chromatography (hexanes/EtOAc 100:1 v/v) afforded the desired product.

¹H NMR (300 MHz, DMSO-d₆) δ 8.88 (s, 1 H).

Intermediate 22**3-Bromo-5-[(5-methyl-1H-pyrazol-3-yl)amino]pyrazine-2-carbonitrile**

3-Bromo-5-chloropyrazine-2-carbonitrile (**Intermediate 21**, 272 mg, 1.25 mmol) and 5-methyl-1H-pyrazol-3-amine (134 mg, 1.38 mmol) were dissolved in dioxane (2 mL) and DIPEA (0.44 mL, 2.50 mmol) was added. The reaction mixture was then heated at 60°C overnight. The reaction mixture was triturated with Et₂O and filtered. The title compound was isolated as a pale orange solid and used in the next step without any further purification.

LCMS: [M+H]⁺ 280.

Intermediate 23**2-Amino-3-cyano-5-methyl-1N-pyrazine oxide**

To a solution of isonitrosoacetone (1.74 g) in *i*-PrOH (30 mL) was added aminomalononitrile *p*-toluenesulfonate (5.0 g) and the resulting mixture was stirred overnight at room temperature. The title compound started to precipitate 10 minutes after complete dissolution of the starting materials had occurred, and was collected by filtration the next day.

¹H NMR (300 MHz, MeOD) δ 8.29 (s, 1 H) 2.36 (s, 3 H).

Intermediate 24**3-Amino-5-chloro-6-methylpyrazine-2-carbonitrile**

To a solution of 2-Amino-3-cyano-5-methyl-1N-pyrazine oxide (**Intermediate 23**, 1.5 g) in DMF (15 ml) was added POCl₃ (3ml), at 0°C, at such a rate that the internal temperature did not

exceed 5°C. The resulting dark solution was heated to 80°C for 2 hours. The solution was cooled to room temperature and was poured, with caution, into ice with vigorous stirring. The resulting suspension was stirred overnight at room temperature. The title compound was isolated by filtration.

LCMS: $[M+H]^+$ 169.

Intermediate 25

3-Bromo-5-chloro-6-methylpyrazine-2-carbonitrile

A solution of 3-amino-5-chloro-6-methylpyrazine-2-carbonitrile (**Intermediate 24**, 0.07 g, 0.42 mmol) in DMF (2 ml) was added drop-wise to a solution of CuBr₂ (0.11 g, 0.5 mmol) and *t*-BuONO (0.13 g, 1.25 mmol) in DMF at 65°C. The resulting mixture was heated at this temperature for 30 minutes and then poured into ice-water. The aqueous layer was extracted with EtOAc and the combined organic layers were dried (Na₂SO₄) and evaporated, providing a solid. Purification by column chromatography (hexanes/EtOAc 50:3 v/v) afforded the desired product.

¹H NMR (300 MHz, DMSO-*d*₆) δ 2.63 (s, 3 H).

Intermediate 26

3-Bromo-6-methyl-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile

3-Bromo-5-chloro-6-methylpyrazine-2-carbonitrile (**Intermediate 25**) and 5-methyl-1*H*-pyrazol-3-amine were reacted using a procedure similar to the one described for the synthesis of **Intermediate 22**, providing the title compound.

LCMS: $[M+H]^+$ 294

Intermediate 27

6-Chloro-*N*-[(1*S*)-1-(4-fluorophenyl)ethyl]pyrazin-2-amine

A microwave reaction vessel charged with 2,6-dichloropyrazine (1.0 g, 6.71 mmol), DIPEA (2.4 mL, 13.42 mmol) and (1*S*)-1-(4-fluorophenyl)ethylamine (0.93 g, 6.71 mmol) in NMP (5 mL) was heated at 180°C for 6 hours. The resulting dark solution was purified by column chromatography (Biotage column, EtOAc/hexanes 30:70 v/v), providing the title compound.

LCMS: $[M+H]^+$ 253.

¹H NMR (300 MHz, DMSO-*d*₆) δ: 1.44 (d, 3 H) 4.73 - 5.18 (m, 1 H) 7.09 - 7.25 (m, 2 H) 7.34 -

7.50 (m, 2 H) 7.68 (s, 1 H) 7.89 (s, 1 H) 8.04 (d, 1 H).

Intermediate 28

1-(5-Fluoropyridin-2-yl)ethanol

To a solution of 5-fluoropyridine-2-carbaldehyde (2.5 g) in Et₂O (50 ml) at 0°C was added dropwise a solution of MeMgBr (8 ml, 3.0M in Et₂O). The resulting solution was stirred at this temperature for 30 minutes and then was allowed to warm to ambient temperature over 1 hour. The mixture was quenched with a solution of saturated NH₄Cl_(aq) and extracted with Et₂O. The organic extracts were dried and evaporated to give the title compound (2.6 g).

¹H NMR δ 8.43 (s, 1H), 7.69 (m, 1H), 7.55 (m, 1H), 5.40 (d, 1H), 4.71 (m, 1H), 1.33 (d, 3H).

Intermediate 29

Ethyl 3,5-difluoropyridine-2-carboxylate

3,5-Difluoropyridine-2-carbonitrile (3.5g, 25mmol) was dissolved in EtOH (50mL) and 4N HCl/1,4-dioxane (50mL) was added. This reaction mixture was refluxed for 24 hours under a nitrogen atmosphere. The reaction mixture was concentrated, dissolved in ethyl acetate (100mL), 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 (3.1g, 69%) as a semi solid.

LCMS: [M+H]⁺188.

Intermediate 30

3,5-Difluoropyridin-2-yl)methanol

A stirred solution of ethyl 3,5-difluoropyridine-2-carboxylate (**Intermediate 29**, 3.1g, 16.57mmol) in anhydrous THF (100mL) was cooled to 0°C. To this solution was added portionwise LiBH₄ (1.1g, 50mmol) under a nitrogen atmosphere. After stirring 30 minutes 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 remaining was diluted with H₂O and extracted with EtOAc (2x). The combined organic phases were dried (Na₂SO₄) and evaporated to give the title compound (1.7g, 71%).

LCMS: $[M+H]^+$ 146.

Intermediate 31

3,5-Difluoropyridine-2-carbaldehyde

To a stirred solution of 3,5-difluoropyridin-2-yl)methanol (**Intermediate 30**, 1.7g, 11.72mmol) in DCM (100mL) was added Dess-Martin periodinane (DMP) (8.45g, 19.92mmol). The resulting solution was stirred at room temperature overnight under a nitrogen atmosphere. The reaction mixture was diluted with DCM, and washed with saturated NaHCO_3 (2x), H_2O and brine. The organic layer was dried over Na_2SO_4 , and concentrated. Purification by column chromatography (EtOAc:Hexane = 2:8) provided the title compound (1.4g, 80%) as a thick oil.

LCMS: $[M+H]^+$ 144.

Intermediate 32

N-[(1-*E* and/or -*Z*)-(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 7** using 3,5-difluoropyridine-2-carbaldehyde (**Intermediate 31**) as a starting material.

LCMS: $[M+H]^+$ 247.

Intermediate 33

N-[1-(3,5-Difluoropyridin-2-yl)ethyl]-2-methylpropane-2-sulfinamide

N-[(1-*E* and/or -*Z*)-(3,5-Difluoropyridin-2-yl)methylene]-2-methylpropane-2-sulfinamide (**Intermediate 32**, 2.5g, 9.6mmol) was dissolved in anhydrous TBME (40mL) and cooled to -78°C . The resulting solution was treated drop-wise with a MeMgBr solution (6.4mL of 3M in Et_2O , 19.2mmol) at -78°C under a nitrogen atmosphere. After stirring for 2 hours at -78°C , the reaction mixture was quenched with saturated NH_4Cl (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 Na_2SO_4 and concentrated. Purification by column chromatography (Hexanes: EtOAc = 1:1) provided the title compound (2.0g, 78%) as a slightly yellow oil.

LCMS: $[M+H]^+$ 263.

Intermediate 34**1-(3,5-Difluoropyridin-2-yl)ethanamine hydrochloride**

To a stirred solution of *N*-[1-(3,5-Difluoropyridin-2-yl)ethyl]-2-methylpropane-2-sulfinamide (**Intermediate 33**, 2.0g, 7.60mmol) in ethyl acetate (25mL) was added 4N HCl in dioxane (7mL) under a nitrogen atmosphere. After stirring for 2 hours at room temperature, the reaction mixture was diluted with TBME (20mL) and product precipitate was filtered, washed with TBME, and dried to obtain the title compound (850mg, 60%) as a white solid.

Intermediate 35***N*-[(1*E* and/or *Z*)-(5-fluoropyridin-2-yl)methylene]-2-methylpropane-2-sulfinamide**

5-Fluoro-2-formylpyridine (5g, 40mmol) and racemic *t*-butyl sulfinamide (9.7g, 80mmol) were dissolved in DCM (100mL). CuSO₄ (12.8g, 80mmol) was added to the reaction mixture. The reaction mixture was stirred overnight at room temperature under a 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*, providing a light yellow oil, which was purified by column chromatography (Hexane/EtOAc = 80:20) to provide the title compound(s) (7.2g, 82%) as a white solid.

LCMS: [M+H]⁺ 229.

Intermediate 36***N*-[1-(5-Fluoropyridin-2-yl)ethyl]-methylpropane-2-sulfinamide**

The title compound was prepared using a process similar to the one described for the synthesis of **Intermediate 8** using *N*-[(1*E* and/or *Z*)-(5-fluoropyridin-2-yl)methylene]-2-methylpropane-2-sulfinamide (**Intermediate 35**) as a starting material.

LCMS: [M+H]⁺ 246.

Intermediate 37**1-(5-Fluoropyridin-2-yl)ethanamine hydrochloride**

The title compound was prepared using a procedure similar to the one described for the synthesis of **Intermediate 5**, using *N*-[1-(5-fluoropyridin-2-yl)ethyl]-methylpropane-2-sulfinamide

(**Intermediate 36**) as a starting material.

LCMS: $[M+H]^+$ 142.

Intermediate 38:

3-Bromo-5-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrazine-2-carbonitrile

A solution of 3-bromo-5-chloropyrazine-2-carbonitrile (**Intermediate 21**, 500 mg, 2.29 mmol), 5-cyclopropyl-1H-pyrazol-3-amine (310 mg, 2.52 mmol), and diisopropylethyl amine (0.600 mL, 3.43 mmol) in dioxane (6 mL) was heated to 60 °C. As the reaction progressed, an orange precipitate formed. The reaction was quenched with water and concentrated to dryness. A suspension resulted from the addition of ethyl acetate, and the resulting heterogenous mixture was filtered. The solids collected were washed with ethyl acetate, followed by a final hexanes wash to give the title compound (473 mg).

^1H NMR (300 MHz, DMSO- d_6) δ : 12.35 (s, 1 H) 11.05 (s, 1 H) 8.42 (s, 1 H) 6.10 (s, 1 H) 1.79 - 2.06 (m, 1 H) 0.93 (d, $J=6.78$ Hz, 2 H) 0.68 (d, $J=4.52$ Hz, 2 H).

LCMS: $[M+H]^+$ 306/308.

Intermediate 39

tert-Butyl-3-amino-5-isopropoxy-1H-pyrazole-1-carboxylate

5-Isopropoxy-1H-pyrazol-3-amine (**Intermediate 40**) and Boc_2O were reacted using a procedure similar to the one described for the synthesis of **Intermediate 18**, providing the title compound.

LCMS: $[M+H]^+$: 242.

Intermediate 40

5-Isopropoxy-1H-pyrazol-3-amine

The title compound was prepared using the procedure described in WO2006/082392.

Intermediate 41

1-(5-Fluoro-pyridine-2-yl)-ethanone

To a stirred solution of isopropylmagnesium chloride (2M solution in THF, 355 mL, 0.71 mol, 1.25 mol eq) in toluene (400 mL), a solution of 2-bromo-5-fluoropyridine (100 g, 0.568 mol, 1.0 mol eq) in toluene (100 mL) was added drop-wise at 25-30 °C and stirred for 1 hour. The reaction

mass was cooled to 5-10 °C and *N*-methoxy-*N*-methylacetamide (70.3 g, 74 ml, 0.682 mol, 1.2 mol eq) was added drop-wise and the reaction mass was stirred at 5-10 °C for 4 hours. The reaction was quenched with a solution of ammonium chloride (182.2 g, 3.408 mol, 6 mol eq) in water (600 ml) and warmed to 35 °C. The organic layer was concentrated under atmospheric distillation. The concentrated residue was fractionally distilled under vacuum to obtain the title compound as a pale yellow liquid (42.96 g, 54.31%).

¹H NMR (CDCl₃, 300MHz) δ 2.68 (s, 3H), 7.50 (ddd, 1H), 8.08 (dd, 1H), 8.48 (d, 1H).

Intermediate 41 (Alternative Procedure)

1-(5-Fluoro-pyridine-2-yl)-ethanone

To a solution of *n*-BuLi (1.6 M in Hexane, 39.06 ml, 0.063 mol, 1.1 mol eq), a solution of 2-bromo-5-fluoropyridine (10.0 g, 0.057 mol, 1.0 mol eq) in toluene (50 ml) was added slowly at -70 °C followed by *N,N*-dimethylacetamide (5.45 g, 5.85 ml, 0.063 mol, 1.1 mol eq) maintaining temperature below -50 °C. The reaction mass was quenched with methanol (2.54 ml), warmed to 5-10 °C and treated with aqueous ammonium chloride (15.2 g, 0.284 mol, 5 mol eq in 60 ml water) solution and stirred at 25-30 °C. The organic layer was washed with water and concentrated under atmospheric distillation to obtain a brown toluene solution of the title compound (5.35 g, 67.64%).

Intermediate 42

[(1*E*)-1-(5-Fluoropyridin-2-yl)ethylidene][(1*S*)-1-phenylethyl]amine

To a stirred solution of 1-(5-fluoropyridin-2-yl)ethanone (**Intermediate 41**, 5.0 g, 0.036 mol, 1.00 mol eq) in toluene (40 ml), (S)-(-)-(α)-methylbenzylamine (4.79 g, 0.04 mol, 1.1 mol eq) was added followed by *p*-toluene sulphonic acid (0.68 g, 0.004 mol, 0.1 mol eq). The reaction mass was refluxed for 5 hours under continuous removal of water using a Dean and Stark apparatus. The reaction mass was cooled and the precipitated solid was filtered off. The organic layer was concentrated using a rotavapor to obtain [(1*E*)-1-(5-fluoropyridin-2-yl)ethylidene][(1*S*)-1-phenylethyl]amine as a brownish yellow oil (7.72 g, 88.63 %).

¹H NMR (CDCl₃, 300MHz) δ 1.55 (d, 3H), 2.42 (s, 3H), 4.91 (q, 1H), 7.28-7.50 (m, 6H), 8.31 (dd, 1H), 8.43 (d, 1H).

Intermediate 43[(1S)-1-(5-Fluoropyridin-2-yl)ethyl][(1S)-1-phenylethyl]amine 2,3-dihydroxysuccinate

To a solution of [(1E)-1-(5-fluoropyridin-2-yl)ethylidene][(1S)-1-phenylethyl]amine (**Intermediate 42**, 2.0 g, 0.008 mol, 1.0 mol eq) in methanol (20 ml), cerium chloride heptahydrate ($\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$) (1.53 g, 0.004 mol, 0.5 mol eq) was added and cooled to -45°C . Sodium borohydride (0.62 g, 0.16 mol, 2.0 mol eq) was added at -45°C and stirred for 15 minutes. The reaction mass was warmed to room temperature and diluted with methylene chloride (30 ml). The organic layer was washed with saturated ammonium chloride solution and the aqueous layer was extracted thrice with methylene chloride (25 ml X 3). The combined organic layer was dried over anhydrous sodium sulphate and concentrated in a rotavapor. The oily residue was dissolved in ethanol (7 ml) and a solution of (L)-Tartaric acid (1.35 g, 0.009 mol, 1.1 mol eq) in ethanol (10 ml) was added to it and stirred over night at ambient temperature. The precipitated solid was filtered and washed with ethanol (5 ml). The white solid was dried in a vacuum oven at 40°C for 1 hour to obtain [(1S)-1-(5-fluoropyridin-2-yl)ethyl][(1S)-1-phenylethyl]amine 2,3-dihydroxysuccinate as a white solid (1.33 g, 40.9%).

^1H NMR (CD_3OD , 300MHz) δ 0.76(d, 3H), 0.89 (d, 3H), 3.33-3.39 (m, 2H), 3.66 (s, 2H), 6.44-6.52(m, 3H), 6.64-6.70(m, 3H), 6.88(ddd, 1H), 7.85(d, 1H).

Intermediate 44(2R)-hydroxy(phenyl)acetic acid - [(1S)-1-(5-fluoropyridin-2-yl)ethyl]amine (1:1)

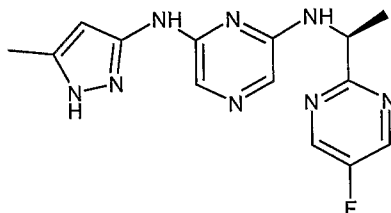
20 % Palladium hydroxide on carbon (wet, approx. 50 % moisture) (1.25 g, 2.5 % w/w) was charged into a 2.0 L Buchi hydrogenation apparatus under nitrogen blanket. A solution of [(1S)-1-(5-fluoropyridin-2-yl)ethyl][(1S)-1-phenylethyl]amine 2,3-dihydroxysuccinate (**Intermediate 43**, 50.0 g 0.127 mol, 1.0 mol eq) and citric acid (60.89 g, 0.317 mol, 2.5 mol eq) in methanol (650 ml, dissolved by heating in water bath) was added followed by washing with methanol (100 ml). The reaction mass was flushed with nitrogen (5 times) followed by hydrogen (5 times) and allowed to stir at 1000 RPM under 4-4.5 Kg hydrogen pressure at 50°C for 11 hours. The reaction mass was cooled to $20-25^\circ\text{C}$, unloaded from the reactor and filtered through a pad of celite followed by washing with 125 ml of methanol. The filtrate was concentrated to 100 ml in a rota-vapor and diluted with water (150 ml). The mass was made alkaline (pH 10-12) by adding an aqueous solution of NaOH (50.71 g, 1.268 mol, 10.0 mol eq in 250 ml of water) at $5-20^\circ\text{C}$.

The organic layer was extracted in ethyl acetate (500 ml X 3) and the combined organic layer was concentrated to 100 ml using a rota-vapor. The oily liquid was again dissolved in 500 ml ethyl acetate and concentrated to 100 mL. The concentrated solution was again diluted with 300 ml of ethyl acetate and added to a solution of with (R)-mandelic acid (21.22 g, 0.139 mol, 1.1 mol eq) in ethyl acetate (150 ml) at 65-70°C and stirred for 15-20 minutes. The mass was cooled to 25-30°C and stirred for 1.5 hours. The precipitated white solid was filtered, washed with ethyl acetate (100 ml) and suck-dried under vacuum. The wet cake was dried in a vacuum oven at 50°C for 1.5 hours to obtain (2*R*)-hydroxy(phenyl)acetic acid - [(1*S*)-1-(5-fluoropyrimidin-2-yl)ethyl]amine as a white solid (28.79 g, 77.68%).

¹H NMR (DMSO-*d*₆-D₂O, 300MHz) δ 1.43(d, 3H), 4.44(q, 1H), 4.54(s, 1H), 7.10-7.25(m, 3H), 7.25-7.39(m, 2H), 7.52(dd, 1H), 7.71(ddd, 1H), 8.53(d, 1H).

Example 1

N-[(1*S*)-1-(5-Fluoropyrimidin-2-yl)ethyl]-*N'*-(5-methyl-1*H*-pyrazol-3-yl)pyrazine-2,6-diamine



A reaction vessel was charged with 6-chloro-*N*-[(1*S*)-1-(5-fluoropyrimidin-2-yl)ethyl]pyrazin-2-amine (**Intermediate 9**, 118 mg, 0.47 mmol), *tert*-butyl 3-amino-5-methyl-1*H*-pyrazole-1-carboxylate (**Intermediate 10**, 103 mg, 0.52 mmol), Cs₂CO₃ (459 mg, 1.14 mmol), Xantphos (14 mg, 0.024 mmol) and Pd₂(dba)₃ (7 mg, 0.012 mmol) and purged with nitrogen for 10 minutes. Dioxane (0.15 M) was then added to the tube and the reaction mixture was purged with nitrogen for another 10 minutes. The reaction mixture was heated at 100°C overnight. The reaction mixture was filtered through a plug of diatomaceous earth, diluted with EtOAc, washed with NaHCO₃(aq) and brine, and dried (Na₂SO₄). The solvent was removed *in vacuo* to give a yellow residue (181 mg), which was purified with a Gilson column (10-35% MeCN/H₂O, 15 min). The title compound was collected as a yellow solid (18.9 mg).

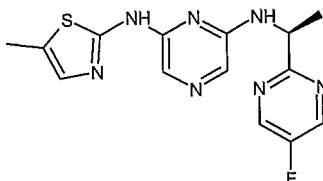
LCMS: [M+H]⁺ 315.

¹H NMR (300 MHz, DMSO-*d*₆) δ: 9.69 (s, 1 H) 8.94 (s, 2 H) 7.77 (br.s, 1 H) 7.53 (s, 1 H) 7.43

(s, 1 H) 6.03 (s, 1 H) 5.68 (s, 1 H) 5.24 (m, 1 H) 2.27 (s, 3 H) 1.60 (d, 3 H).

Example 2

N-[(1*S*)-1-(5-Fluoropyrimidin-2-yl)ethyl]-*N'*-(5-methyl-1,3-thiazol-2-yl)pyrazine-2,6-diamine



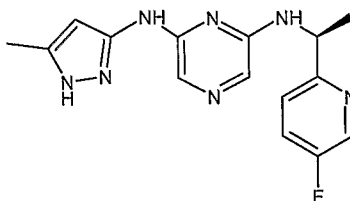
6-Chloro-*N*-[(1*S*)-1-(5-fluoropyrimidin-2-yl)ethyl]pyrazin-2-amine (**Intermediate 9**) and 5-methyl-1,3-thiazol-2-amine were reacted using a procedure similar to the one described for the synthesis of **Example 1**, providing the title compound.

LCMS: $[M+H]^+$ 332.

^1H NMR (300 MHz, DMSO- d_6) δ : 9.03 - 9.12 (br.s, 1 H) 8.87 (s, 2 H) 7.67 (br.s, 1 H) 7.56 (s, 1 H) 7.43 (s, 1 H) 6.99 (d, 1 H) 5.29 - 5.46 (m, 1 H) 2.28 (d, 3 H) 1.58 (d, 3 H).

Example 3

N-[(1*S*)-1-(5-Fluoropyridin-2-yl)ethyl]-*N'*-(5-methyl-1*H*-pyrazol-3-yl)pyrazine-2,6-diamine



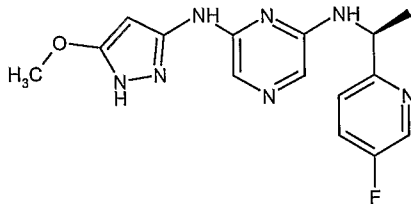
6-Chloro-*N*-[(1*S*)-1-(5-fluoropyridin-2-yl)ethyl]pyrazin-2-amine (**Intermediate 16**) and *tert*-butyl 3-amino-5-methyl-1*H*-pyrazole-1-carboxylate (**Intermediate 10**) were reacted using a procedure similar to the one described for the synthesis of **Example 1**, providing the title compound.

LCMS: $[M+H]^+$ 314.

^1H NMR (300 MHz, DMSO- d_6) δ : ppm 9.49 (s, 1 H) 8.46 (s, 1 H) 7.61 (m, 2 H) 7.40 (m, 1 H) 7.27 (s, 1 H) 5.81 (s, 1 H) 4.88 - 5.05 (m, 1 H) 2.13 (s, 3 H) 1.43 (d, 3 H).

Example 4

N-[(1*S*)-1-(5-Fluoropyridin-2-yl)ethyl]-*N'*-(5-methoxy-1*H*-pyrazol-3-yl)pyrazine-2,6-diamine



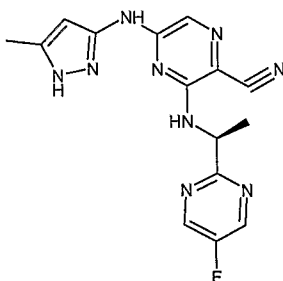
6-Chloro-*N*-[(1*S*)-1-(5-fluoropyridin-2-yl)ethyl]pyrazin-2-amine (**Intermediate 16**) and *tert*-butyl 3-amino-5-methoxy-1*H*-pyrazole-1-carboxylate (**Intermediate 18**) were reacted using a procedure similar to the one described for the synthesis of **Example 1**, providing the title compound.

LCMS: $[M+H]^+$ 330.

^1H NMR (300 MHz, DMSO- d_6) δ : 1.50 (d, 3 H) 3.78 (s, 3 H) 4.86 - 5.04 (m, 1 H) 5.32 (s, 1 H) 7.27 (s, 1 H) 7.31 (s, 1 H) 7.48 (dd, 1 H) 7.66 - 7.74 (ddd, 1 H) 8.49 (d, 1 H) 9.73 (s, 1 H).

Example 5

3-([(1*S*)-1-(5-Fluoropyrimidin-2-yl)ethyl]amino)-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile



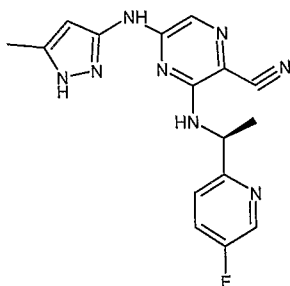
A microwave reaction vessel was charged with 3-bromo-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile (**Intermediate 22**), 100 mg, 0.36 mmol), (1*S*)-1-(5-fluoropyrimidin-2-yl)ethanamine hydrochloride (**Intermediate 5**, 70 mg, 0.39 mmol) and DIPEA (0.20 mL, 1.17 mmol). Isoamyl alcohol (1 mL) was then added and the tube was sealed and heated at 160°C for 14400 seconds in a microwave reactor. The solvent mixture was removed in vacuo leaving a brown solid (271 mg). This material was purified using a Gilson column (5-95% MeCN/H₂O, 35 min) providing the title compound as a yellow solid (54.1 mg).

LCMS: $[M+H]^+$ 338.

^1H NMR (300 MHz, DMSO- d_6) δ : 10.16 (s, 1 H) 8.83 (d, 2 H) 7.49 (s, 1 H) 7.29 (d, 1 H) 5.92 (s, 1 H) 5.14 - 5.31 (m, 1 H) 2.09 - 2.18 (s, 3 H) 1.55 (d, 3 H).

Example 6

3-([(1*S*)-1-(5-fluoropyridin-2-yl)ethyl]amino}-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile



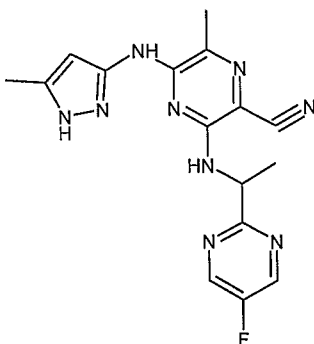
3-Bromo-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile (**Intermediate 22**) and (1*S*)-1-(5-fluoropyridin-2-yl)ethanamine (**Intermediate 15**) were reacted using a procedure similar to the one described for the synthesis of **Example 5**, providing the title compound.

LCMS: $[M+H]^+$ 339.

^1H NMR (300 MHz, DMSO- d_6) δ : 10.29 (s, 1 H) 8.54 (d, 1 H) 7.63 - 7.75 (m, 1 H) 7.44 - 7.61 (m, 3 H) 5.95 - 6.05 (s, 1 H) 5.12 - 5.30 (m, 1 H) 2.15 - 2.25 (s, 3 H) 1.56 (d, 3 H).

Example 7

3-{1-(5-Fluoropyrimidin-2-yl)ethyl}amino}-6-methyl-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile



3-Bromo-6-methyl-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile (**Intermediate 26**) and (1*S*)-1-(5-fluoropyrimidin-2-yl)ethanamine hydrochloride (**Intermediate 5**) were reacted

using a procedure similar to the one described for the synthesis of **Example 5**. Chiral analysis of the final product indicated that partial racemization of the resulting compound had occurred.

Column and solvent conditions

The R and S enantiomers of the title compound were chirally separated using a Gilson HPLC Chiral Purification system.

Column type, particle size: Chiralpak AD, 20 μ
Column dimensions (mm): 50 x 500
Mobile phase: 50 % Hexane, 50 % 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, 10 μ
Column dimensions (mm): 4.6 x 250
Mobile phase: 50 % Hexane, 50 % Isopropanol, 0.1 % diethylamine
Flow rate (ml/min): 1

Example 7(a), First Eluting Compound

3-{1-(5-Fluoropyrimidin-2-yl)ethyl}amino}-6-methyl-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile, enantiomer A

The first eluting compound had a retention time of 4.67 minutes (e.e. >98%).

LCMS: $[M+H]^+$ 354

^1H NMR (300 MHz, DMSO- d_6) δ : 9.18 (s, 1 H) 8.88 (s, 2 H) 7.13 (d, 1 H) 5.96 (s, 1 H) 5.18 - 5.31 (m, 1 H) 2.26 - 2.32 (s, 3 H) 2.21 (s, 3 H) 1.59 (d, 3 H).

Example 7(b,) Second Eluting Compound

3-{1-(5-Fluoropyrimidin-2-yl)ethyl}amino}-6-methyl-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile, enantiomer B

The second eluting compound had a retention time of 7.24 minutes (e.e. > 98%).

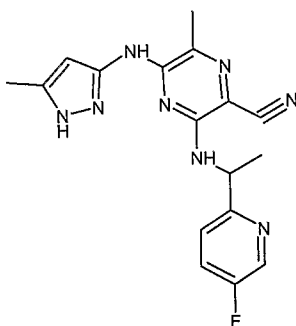
LCMS: 354 $[M+H]$.

¹H NMR (300 MHz) δ : 8.72 (d, 2 H) 6.27 (s, 1 H) 5.21 - 5.42 (m, 1 H) 2.34 (s, 6 H) 1.65 (d, 3 H).

Enantiomeric excess for each enantiomer of **Example 7** was calculated using area percent at 220 nm.

Example 8

3-{[1-(5-Fluoropyridin-2-yl)ethyl]amino}-6-methyl-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile



3-Bromo-6-methyl-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile (**Intermediate 26**) and (1*S*)-1-(5-fluoropyridin-2-yl)ethanamine (**Intermediate 15**) were reacted using a procedure similar to the one described for the synthesis of **Example 5**. Chiral analysis of the final product indicated that partial racemization of the resulting compound had occurred.

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 12.05 (s, 1 H) 9.11 (s, 1 H) 8.52 (d, 1 H) 7.55 - 7.77 (m, 1 H) 7.43 (dd, 1 H) 7.22 (d, 1 H) 5.89 (s, 1 H) 4.98 - 5.27 (m, 1 H) 2.23 - 2.31 (m, 3 H) 1.51 (d, 3 H)

Column and solvent conditions

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

Column type, particle size: Chiralcel OJ-H, 5 μ

Column dimensions (mm): 21x 250

Modifier / additive: 20 % Methanol

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 Diode Array.

Column type/particle size: Chiralcel OJ-H, 5 μ
Column dimensions (mm): 100 x 4.6
Modifier / additive: 10 % Methanol
Flow rate (ml/min): 5
Oven (°C): 35
Outlet Pressure (bar): 120

Example 8(a), First Eluting Compound

3-{{[1-(5-Fluoropyridin-2-yl)ethyl]amino}-6-methyl-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile, Enantiomer A

The first eluting compound had a retention time of 1.04 minutes (e.e. >98 %).

LCMS: 353 [M+1]

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 12.05 (s, 1 H) 9.11 (s, 1 H) 8.52 (d, 1 H) 7.55 - 7.77 (m, 1 H) 7.43 (dd, 1 H) 7.22 (d, 1 H) 5.89 (s, 1 H) 4.98 - 5.27 (m, 1 H) 2.23 - 2.31 (m, 3 H) 1.51 (d, 3 H).

Example 8(b), Second Eluting Compound

3-{{[1-(5-Fluoropyridin-2-yl)ethyl]amino}-6-methyl-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile, Enantiomer B

The second eluting compound had a retention time of 1.56 minutes (e.e. >98 %).

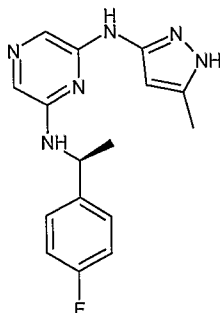
LCMS: 353 [M+1]

¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 12.05 (s, 1 H) 9.11 (s, 1 H) 8.52 (d, 1 H) 7.55 - 7.77 (m, 1 H) 7.43 (dd, 1 H) 7.22 (d, 1 H) 5.89 (s, 1 H) 4.98 - 5.27 (m, 1 H) 2.23 - 2.31 (m, 3 H) 1.51 (d, 3 H).

Enantiomeric excess for each enantiomer of **Example 8** was calculated using area percent at 220 nm.

Example 9

N-[(1*S*)-1-(4-Fluorophenyl)ethyl]-*N'*-(5-methyl-1*H*-pyrazol-3-yl)pyrazine-2,6-diamine



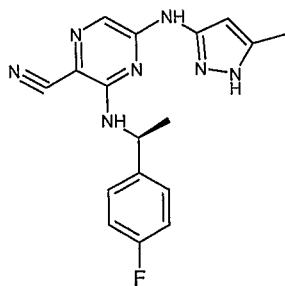
6-Chloro-*N*-[(1*S*)-1-(4-fluorophenyl)ethyl]pyrazin-2-amine (**Intermediate 27**) and 5-methyl-1*H*-pyrazol-3-amine were reacted using a procedure similar to the one described for the synthesis of **Example 5**, providing the title compound.

LCMS: $[M+H]^+$ 313.

^1H NMR (300 MHz, DMSO- d_6) δ : 1.46 (d, 3 H) 2.17 (s, 3 H) 4.81 - 5.15 (m, 1 H) 5.97 (s, 1 H) 7.10 - 7.17 (m, 2 H) 7.27 (s, 1 H) 7.38 - 7.45 (m, 2 H) 7.49 (s, 1 H) 7.59 - 7.67 (m, 1 H) 9.60 (s, 1 H).

Example 10

3-{[(1*S*)-1-(4-Fluorophenyl)ethyl]amino}-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile



3-Bromo-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile (**Intermediate 22**) and (1*S*)-1-(4-fluorophenyl)ethanamine were reacted using a procedure similar to the one described

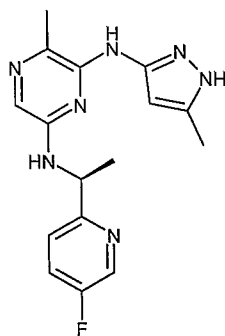
for the synthesis of **Example 5**, providing the title compound.

LCMS: $[M+H]^+$ 338.

^1H NMR (300 MHz, DMSO- d_6) δ : 1.49 (d, 3 H) 2.18 (s, 3 H) 5.12 - 5.15 (m, 1 H) 5.93 (s, 1 H) 7.13 - 7.17 (m, 2 H) 7.26 (s, 1 H) 7.40 - 7.45 (m, 2 H) 7.55 - 7.59 (m, 1 H) 9.93 (s, 1 H).

Example 11

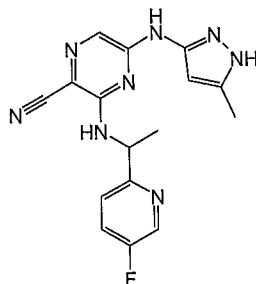
*N*⁶-[(1*S*)-1-(5-fluoropyridin-2-yl)ethyl]-3-methyl-*N*²-(5-methyl-1*H*-pyrazol-3-yl)pyrazine-2,6-diamine



3-[[[(1*S*)-1-(5-fluoropyridin-2-yl)ethyl]amino]-5-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyrazine-2-carbonitrile (**Example 8**, 109 mg, 0.31 mmol) was dissolved in MeOH (2 mL) and 5*N* HCl (5 mL) was added. The reaction was heated at 100°C for 48 hours. LCMS showed ~50% formation of the product ($m+1=328$). The reaction mixture was then concentrated *in vacuo* leaving a yellow solid (75 mg). This material was purified with a Gilson column (5-40% MeCN/H₂O, 9 min). Concentration of the fractions *in vacuo* gave the title compound as a yellow solid (39 mg).

LCMS: $[M+H]^+$ 328

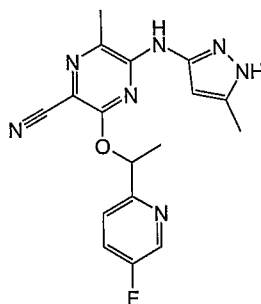
^1H NMR (300 MHz DMSO- d_6) δ : 9.20 (s, 1 H) 8.51 (d, 1 H) 7.53 - 7.80 (m, 2 H) 7.44 (dd, 1 H) 7.25 (s, 1 H) 5.99 (s, 1 H) 4.88 - 5.03 (m, 2 H) 2.30 (s, 3 H) 2.23 (s, 3 H) 1.49 (d, 3 H).

Example 12**3-(1-(5-Fluoropyridin-2-yl)ethylamino)-5-(5-methyl-1H-pyrazol-3-ylamino)pyrazine-2-carbonitrile**

3-Bromo-5-(5-methyl-1H-pyrazol-3-ylamino)pyrazine-2-carbonitrile (**Intermediate 22**, 49 mg, 0.18 mmol) and 1-(5-fluoropyridin-2-yl)ethanamine hydrochloride (**Intermediate 37**, 34.1 mg, 0.19 mmol) were dissolved in isoamyl alcohol (1 mL). DIPEA (0.092 mL, 0.53 mmol) was added to the reaction mixture. The reaction mixture was then microwaved at 160°C for 14400 seconds. The reaction mixture was filtered and concentrated in vacuo leaving a yellow oil (141 mg). This material was purified using a Gilson column (15-50% MeCN/H₂O, 15 min). Concentration of the fractions in vacuo gave the title compound as a yellow solid (35 mg).

LCMS: [M+H]⁺ 339

¹H NMR (300 MHz, MeOD, δ): 8.40 (s, 1 H) 7.65 - 7.78 (m, 2 H) 7.51 (s, 1 H) 6.11 (s, 1 H) 5.33 (q, 1 H) 2.42 (s, 3 H) 1.70 (d, 3 H)

Example 13**3-(1-(5-Fluoropyridin-2-yl)ethoxy)-6-methyl-5-(5-methyl-1H-pyrazol-3-ylamino)pyrazine-2-carbonitrile**

3-Bromo-6-methyl-5-(5-methyl-1H-pyrazol-3-ylamino)pyrazine-2-carbonitrile (**Intermediate 26**, 200 mg, 0.68 mmol) and 1-(5-fluoropyridin-2-yl)ethanol (**Intermediate 28**, 289 mg, 2.05 mmol) were dissolved in t-BuOH (1.36 mL). Sodium t-butoxide (131 mg, 1.36 mmol) was added to the reaction mixture. The reaction mixture was then heated at 90°C overnight. LCMS showed ~12% formation of the product and ~58% starting material, so another equivalent of 1-(5-fluoropyridin-2-yl)ethanol (96.0 mg, 0.68 mmol) was added, and the reaction was heated again. After 4 hours, LCMS showed no change in the reaction progress, so the reaction mixture was transferred to the microwave and heated at 120°C for 14400s. LCMS showed that the amount of product increased to ~38%. The reaction mixture was concentrated in vacuo leaving a brown oil (591 mg). The material was purified using a Gilson column (50-75% NH₄OH/MeOH, 25 min). Concentration of the fractions in vacuo gave a yellow solid (62.2 mg).

¹H NMR (300 MHz, DMSO-d₆) δ 12.20 (s, 1 H) 9.58 (s, 1 H) 8.37 - 8.74 (m, 1 H) 7.58 - 7.86 (m, 1 H) 7.43 (dd, 1 H) 5.97 - 6.10 (m, 1 H) 5.91 (s, 1 H) 2.36 (s, 3 H) 2.20 (s, 3 H) 1.63 (d, 3 H).

Column and solvent conditions

The R and S enantiomers of the title compound were chirally separated using a Gilson HPLC Chiral Purification system.

Column type, particle size: Chiralcel OJ, 10μ
Column dimensions (mm): 250 x 20
Mobile phase: 70% hexane, 30% isopropanol, 0.1% diethylamine
Flow rate (ml/min): 10

Post purification purity check

Sample purity was checked with a chiral HPLC (Agilent 1100) using a Diode Array.

Column type, particle size: Chiralcel OJ, 10μ
Column dimensions (mm): 250 x 4.6
Mobile phase: 70% hexane, 30% isopropanol, 0.1% diethylamine
Flow rate (ml/min): 0.5

Example 13(a), First Eluting Compound3-(1-(5-Fluoropyridin-2-yl)ethoxy)-6-methyl-5-(5-methyl-1H-pyrazol-3-ylamino)pyrazine-2-carbonitrile, enantiomer A

The first eluting compound had a retention time of 10.8 minutes (e.e. >98 %), and was collected as a pale yellow solid (17.5 mg).

LCMS: $[M+H]^+$ 354.

^1H NMR (300 MHz, DMSO- d_6) δ 12.20 (s, 1 H) 9.58 (s, 1 H) 8.37 - 8.74 (m, 1 H) 7.58 - 7.86 (m, 1 H) 7.43 (dd, 1 H) 5.97 - 6.10 (m, 1 H) 5.91 (s, 1 H) 2.36 (s, 3 H) 2.20 (s, 3 H) 1.63 (d, 3 H).

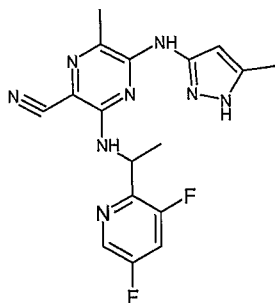
Example 13(b), Second Eluting Compound3-(1-(5-Fluoropyridin-2-yl)ethoxy)-6-methyl-5-(5-methyl-1H-pyrazol-3-ylamino)pyrazine-2-carbonitrile, enantiomer B

The second eluting compound had a retention time of 14.6 minutes (e.e. 96.5%), and was collected as a very pale yellow solid (19.8 mg).

LCMS: $[M+H]^+$ 354.

^1H NMR (300 MHz, DMSO- d_6) δ 12.20 (s, 1 H) 9.58 (s, 1 H) 8.37 - 8.74 (m, 1 H) 7.58 - 7.86 (m, 1 H) 7.43 (dd, 1 H) 5.97 - 6.10 (m, 1 H) 5.91 (s, 1 H) 2.36 (s, 3 H) 2.20 (s, 3 H) 1.63 (d, 3 H).

Enantiomeric excess for each enantiomer of **Example 13** was calculated using area percent at 254 nm.

Example 143-(1-(3,5-Difluoropyridin-2-yl)ethylamino)-6-methyl-5-(5-methyl-1H-pyrazol-3-ylamino)pyrazine-2-carbonitrile

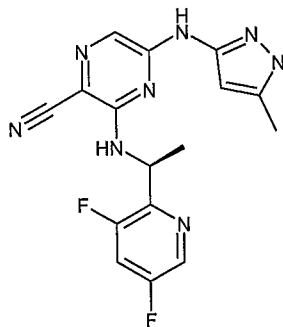
3-Bromo-6-methyl-5-(5-methyl-1H-pyrazol-3-ylamino)pyrazine-2-carbonitrile (**Intermediate 26**, 200 mg, 0.68 mmol) and 1-(3,5-difluoropyridin-2-yl)ethanamine, HCl (**Intermediate 34**, 146 mg, 0.75 mmol) were dissolved in isoamyl alcohol (2 mL). DIPEA (0.358 mL, 2.05 mmol) was added to the mixture. The reaction mixture was then heated at 160°C overnight. The reaction mixture was concentrated in vacuo leaving an amber oil (602 mg). This material was purified using a Gilson column (25-35% ACN/H₂O, 35 min). Concentration of the fractions in vacuo gave the title compound as a yellow solid (88.6 mg).

LCMS: [M+H]⁺ 371

¹H NMR (300 MHz, DMSO-d₆) δ 9.20 (s, 1 H) 8.44 (d, 1 H) 7.85 - 8.02 (m, 1 H) 7.02 (d, 1 H) 6.08 (s, 1 H) 5.34 - 5.53 (m, 1 H) 2.27 (s, 3 H) 2.23 (s, 3 H) 1.49 (d, 3 H)

Example 15

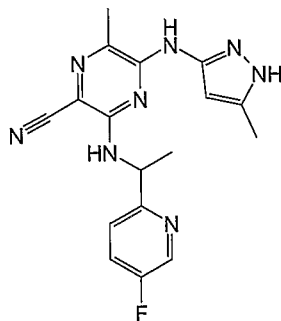
3-([(1R)-1-(3,5-Difluoropyridin-2-yl)ethyl]amino)-5-[(5-methyl-1H-pyrazol-3-yl)amino]pyrazine-2-carbonitrile



A microwave reaction vessel was charged with 3-bromo-5-[(5-methyl-1H-pyrazol-3-yl)amino]pyrazine-2-carbonitrile (**Intermediate 22**, 335 mg, 1.2 mmol), 1-(3,5-difluoropyridin-2-yl)ethanamine hydrochloride (**Intermediate 34**, 234 mg, 1.2 mmol) and DIPEA (0.520 mL, 3.0mmol). n-Butanol (1 mL) was then added and the tube was sealed and heated at 160°C for 7 hours in a microwave reactor. The reaction was concentrated in vacuo leaving a brown solid which was purified using a Gilson column (5-95% MeCN/H₂O, 35 min) giving the title compound as a yellow solid (113.3mg).

LCMS: 357 [M+H].

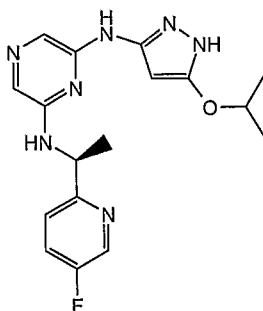
¹H NMR (300 MHz) δ: 8.37 (d, 1 H) 7.54-7.64 (m, 2 H) 6.26 (s, 1 H) 5.63 (q, 1 H) 2.33 (s, 3 H) 1.60(d, 3 H).

Example 16**3-(1-(5-Fluoropyridin-2-yl)ethylamino)-6-methyl-5-(5-methyl-1H-pyrazol-3-ylamino)pyrazine-2-carbonitrile**

3-Bromo-6-methyl-5-(5-methyl-1H-pyrazol-3-ylamino)pyrazine-2-carbonitrile (**Intermediate 26**, 50 mg, 0.17 mmol) and 1-(5-fluoropyridin-2-yl)ethanamine, HCl (**Intermediate 37**, 33.1 mg, 0.19 mmol) were dissolved in isoamyl alcohol (1 mL). DIPEA (0.089 mL, 0.51 mmol) was added to the reaction mixture. The reaction mixture was heated at 160°C overnight. The reaction mixture was concentrated in vacuo leaving a brown oil (169 mg). This material was purified using a Gilson column (20-50% MeCN/H₂O, 15 min). Concentration of the fractions in vacuo gave the title compound as a yellow solid (9.7 mg).

LCMS: 353 [M+1]

¹H NMR (300 MHz, DMSO-d₆) δ 9.15 (s, 1 H) 8.52 (d, 1 H) 7.56 - 7.79 (m, 1 H) 7.44 (dd, 1 H) 7.27 (d, 1 H) 5.90 (s, 1 H) 5.03 - 5.22 (m, 2 H) 2.22 - 2.32 (m, 3 H) 2.18 (s, 3 H) 1.52 (d, 3 H)

Example 17**(S)-N²-(1-(5-Fluoropyridin-2-yl)ethyl)-N⁶-(5-isopropoxy-1H-pyrazol-3-yl)pyrazine-2,6-diamine hydrochloride**

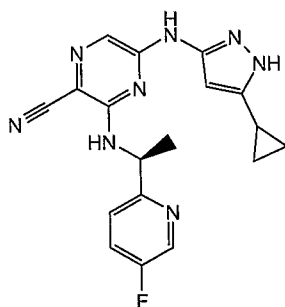
To a solution of (S)-*tert*-butyl 3-(6-(1-(5-fluoropyridin-2-yl)ethylamino)pyrazin-2-ylamino)-5-isopropoxy-1H-pyrazole-1-carboxylate (**Example 19**, 408 mg, 0.89 mmol) in methanol (2 mL) was added HCl (4M in dioxane) (0.892 mL, 3.57 mmol). The solution was allowed to stir at room temperature for 1 hour. The reaction was concentrated to dryness to afford the title salt (350 mg).

LCMS: 358 [M+H].

¹H NMR (300 MHz, DMSO-d₆) δ ppm 8.51 (d, 2 H) 7.68 - 7.80 (m, 1 H) 7.54 (dd, *J*=8.29, 4.52 Hz, 1 H) 7.47 (s, 1 H) 7.43 (s, 1 H) 5.66 (s, 1 H) 5.08 (d, *J*=6.78 Hz, 1 H) 4.56 - 4.72 (m, 1 H) 1.52 (d, 3 H) 1.31 (dd, 6 H).

Example 18

(S)-5-(5-Cyclopropyl-1H-pyrazol-3-ylamino)-3-(1-(5-fluoropyridin-2-yl)ethylamino)pyrazine-2-carbonitrile



A mixture of 3-bromo-5-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrazine-2-carbonitrile (**Intermediate 38**, 150 mg, 0.49 mmol), (1*S*)-1-(5-Fluoropyrimidin-2-yl)ethanamine hydrochloride (**Intermediate 5**, 104 mg, 0.59 mmol), and diisopropyl amine (0.258 mL, 1.47 mmol) in isoamyl alcohol (2.5 mL) was heated at 160 °C for 18 hours. The reaction mixture was evaporated down to a residue and purified directly on a Biotage column (25+M) using 30% to 50% of EtOAc (10%v/v) in CH₂Cl₂. The product collected was further purified on a Gilson column using 5 to 95% MeCN (0.1% TFA) in water (0.1% TFA) over 15 minutes at 254 nm. The collected fractions were lyophilized to afford the title compound (92 mg).

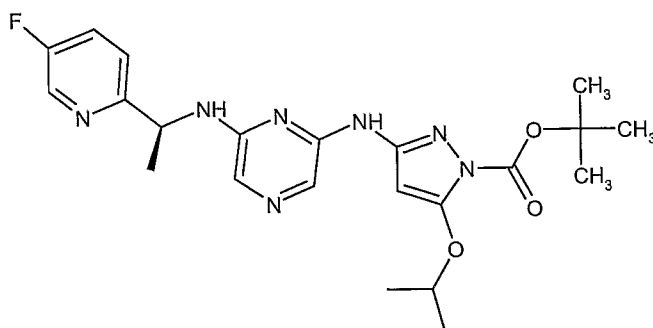
LCMS: [M+H]⁺ 365.

¹H NMR (300 MHz, DMSO-d₆) δ: 10.28 (s, 1 H) 8.50 (d, *J*=3.01 Hz, 1 H) 7.61 - 7.75 (m, 1 H)

7.42 - 7.61 (m, 3 H) 5.99 (s, 1 H) 5.15 - 5.30 (m, 1 H) 1.77 - 1.92 (m, 1 H) 1.55 (d, $J=7.54$ Hz, 3 H) 0.87 - 1.04 (m, 2 H) 0.62 - 0.78 (m, 2 H).

Example 19

(S)-tert-Butyl 3-(6-(1-(5-fluoropyridin-2-yl)ethylamino)pyrazin-2-ylamino)-5-isopropoxy-1H-pyrazole-1-carboxylate



A reaction vessel was charged with (S)-6-chloro-N-(1-(5-fluoropyridin-2-yl)ethyl)pyrazin-2-amine (**Intermediate 16**, 400 mg, 1.58 mmol), tert-butyl 3-amino-5-isopropoxy-1H-pyrazole-1-carboxylate (**Intermediate 39**, 420 mg, 1.74 mmol), $\text{Pd}_2(\text{dba})_3$ (36.2 mg, 0.04 mmol), Xantphos (45.8 mg, 0.08 mmol), Cs_2CO_3 (1.238 g, 3.80 mmol), and dioxane (10.600 mL) under nitrogen. The resulting mixture was degassed and then heated to 100 °C for 16 hours. The residue obtained after concentration *in vacuo* was purified on a Biotage column using 30% to 60% EtOAc in hexanes which afforded the title compound (408 mg).

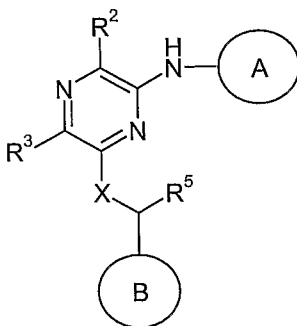
LCMS: $[\text{M}+\text{H}]^+$ 458.

^1H NMR (300 MHz, CHCl_3 - d_3) δ : 9.68 (s, 1 H) 8.42 (s, 1 H) 7.47 (s, 1 H) 7.43 (s, 1 H) 7.29 - 7.36 (m, 2 H) 6.16 (s, 1 H) 5.42 (d, $J=6.03$ Hz, 1 H) 4.99 - 5.12 (m, 1 H) 4.85 - 4.98 (m, 1 H) 1.63 (s, 9 H) 1.58 (d, $J=6.78$ Hz, 3 H) 1.37 (d, , 6 H).

Claims

What is claimed is:

1. A compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is selected from the group consisting of 5- and 6- membered heteroaryl, wherein said 5- and 6- membered heteroaryl are optionally substituted with one or more R^1 ;

Ring B is selected from the group consisting of carbocyclyl and heterocyclyl, wherein said carbocyclyl and heterocyclyl are optionally substituted with one or more R^6 ;

X is selected from the group consisting of -O-, -S-, and -N(R^{4a})-;

R^1 in each occurrence is independently selected from the group consisting of halo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, heterocyclyl, -OR^{1a}, -SR^{1a}, -N(R^{1a})₂, -N(R^{1a})C(O)R^{1b}, -N(R^{1a})N(R^{1a})₂, -NO₂, -C(O)H, -C(O)R^{1b}, -C(O)₂R^{1a}, -C(O)N(R^{1a})₂, -OC(O)N(R^{1a})₂, -N(R^{1a})C(O)₂R^{1a}, -N(R^{1a})C(O)N(R^{1a})₂, -OC(O)R^{1b}, -S(O)R^{1b}, -S(O)₂R^{1b}, -S(O)₂N(R^{1a})₂, -N(R^{1a})S(O)₂R^{1b}, -C(R^{1a})=N(R^{1a}), and -C(R^{1a})=N(OR^{1a}), wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R^{10} ;

R^{1a} in each occurrence is independently selected from the group consisting of H, C_{1-6} alkyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^{10} ;

R^{1b} in each occurrence is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl,

C₂₋₆alkynyl, carbocyclyl, and heterocyclyl, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R¹⁰;

R² is selected from the group consisting of H, halo, -CN, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, heterocyclyl, -OR^{2a}, -SR^{2a}, -N(R^{2a})₂, -N(R^{2a})C(O)R^{2b}, -N(R^{2a})N(R^{2a})₂, -NO₂, -C(O)H, -C(O)R^{2b}, -C(O)₂R^{2a}, -C(O)N(R^{2a})₂, -OC(O)N(R^{2a})₂, -N(R^{2a})C(O)₂R^{2a}, -N(R^{2a})C(O)N(R^{2a})₂, -OC(O)R^{2b}, -S(O)R^{2b}, -S(O)₂R^{2b}, -S(O)₂N(R^{2a})₂, -N(R^{2a})S(O)₂R^{2b}, -C(R^{2a})=N(R^{2a}), and -C(R^a)=N(OR^{2a}), wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R²⁰;

R^{2a} in each occurrence is independently selected from the group consisting of H, C₁₋₆alkyl, carbocyclyl, and heterocyclyl, wherein said C₁₋₆alkyl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R²⁰;

R^{2b} in each occurrence is independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R²⁰;

R³ is selected from the group consisting of H, halo, -CN, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, heterocyclyl, -OR^{3a}, -SR^{3a}, -N(R^{3a})₂, -N(R^{3a})C(O)R^{3b}, -N(R^{3a})N(R^{3a})₂, -NO₂, -C(O)H, -C(O)R^{3b}, -C(O)₂R^{3a}, -C(O)N(R^{3a})₂, -OC(O)N(R^{3a})₂, -N(R^{3a})C(O)₂R^{3a}, -N(R^{3a})C(O)N(R^{3a})₂, -OC(O)R^{3b}, -S(O)R^{3b}, -S(O)₂R^{3b}, -S(O)₂N(R^{3a})₂, -N(R^{3a})S(O)₂R^{3b}, -C(R^{3a})=N(R^{3a}), and -C(R^{3a})=N(OR^{3a}), wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R³⁰;

R^{3a} in each occurrence is independently selected from the group consisting of H, C₁₋₆alkyl, carbocyclyl, and heterocyclyl, wherein said C₁₋₆alkyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R³⁰;

R^{3b} in each occurrence is independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R³⁰;

R^{4a} is selected from the group consisting of H, C_{1-6} alkyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^{40} ;

R^5 is selected from the group consisting of -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, heterocyclyl, $-N(R^{5a})C(O)R^{5b}$, $-N(R^{5a})N(R^{5a})_2$, $-NO_2$, $-C(O)H$, $-C(O)R^{5b}$, $-C(O)_2R^{5a}$, $-C(O)N(R^{5a})_2$, $-OC(O)N(R^{5a})_2$, $-N(R^{5a})C(O)_2R^{5a}$, $-N(R^{5a})C(O)N(R^{5a})_2$, $-OC(O)R^{5b}$, $-S(O)R^{5b}$, $-S(O)_2R^{5b}$, $-S(O)_2N(R^{5a})_2$, $-N(R^{5a})S(O)_2R^{5b}$, $-C(R^{5a})=N(R^{5a})$, and $-C(R^{5a})=N(OR^{5a})$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R^{50} ;

R^{5a} in each occurrence is independently selected from the group consisting of H, C_{1-6} alkyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^{50} ;

R^{5b} in each occurrence is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^{50} ;

R^6 in each occurrence is independently selected from the group consisting of halo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, heterocyclyl, $-OR^{6a}$, $-SR^{6a}$, $-N(R^{6a})_2$, $-N(R^{6a})C(O)R^{6b}$, $-N(R^{6a})N(R^{6a})_2$, $-NO_2$, $-C(O)H$, $-C(O)R^{6b}$, $-C(O)_2R^{6a}$, $-C(O)N(R^{6a})_2$, $-OC(O)N(R^{6a})_2$, $-N(R^{6a})C(O)_2R^{6a}$, $-N(R^{6a})C(O)N(R^{6a})_2$, $-OC(O)R^{6b}$, $-S(O)R^{6b}$, $-S(O)_2R^{6b}$, $-S(O)_2N(R^{6a})_2$, $-N(R^{6a})S(O)_2R^{6b}$, $-C(R^{6a})=N(R^{6a})$, and $-C(R^{6a})=N(OR^{6a})$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are optionally substituted with one or more R^{60} ;

R^{6a} in each occurrence is independently selected from the group consisting of H, C_{1-6} alkyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^{60} ;

R^{6b} in each occurrence is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^{60} ;

R^{10} in each occurrence is independently selected from the group consisting of halo, -CN,

C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, heterocyclyl, -OR^{10a}, -SR^{10a}, -N(R^{10a})₂, -N(R^{10a})C(O)R^{10b}, -N(R^{10a})N(R^{10a})₂, -NO₂, -C(O)H, -C(O)R^{10b}, -C(O)₂R^{10a}, -C(O)N(R^{10a})₂, -OC(O)N(R^{10a})₂, -N(R^{10a})C(O)₂R^{10a}, -N(R^{10a})C(O)N(R^{10a})₂, -OC(O)R^{10b}, -S(O)R^{10b}, -S(O)₂R^{10b}, -S(O)₂N(R^{10a})₂, -N(R^{10a})S(O)₂R^{10b}, -C(R^{10a})=N(R^{10a}), and -C(R^{10a})=N(OR^{10a}), wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^a;

R^{10a} in each occurrence is independently selected from the group consisting of H, C₁₋₆alkyl, carbocyclyl, and heterocyclyl, wherein said C₁₋₆alkyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^a;

R^{10b} in each occurrence is independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^a;

R²⁰ in each occurrence is independently selected from the group consisting of halo, -CN, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, heterocyclyl, -OR^{20a}, -SR^{20a}, -N(R^{20a})₂, -N(R^{20a})C(O)R^{20b}, -N(R^{20a})N(R^{20a})₂, -NO₂, -C(O)H, -C(O)R^{20b}, -C(O)₂R^{20a}, -C(O)N(R^{20a})₂, -OC(O)N(R^{20a})₂, -N(R^{20a})C(O)₂R^{20a}, -N(R^{20a})C(O)N(R^{20a})₂, -OC(O)R^{20b}, -S(O)R^{20b}, -S(O)₂R^{20b}, -S(O)₂N(R^{20a})₂, -N(R^{20a})S(O)₂R^{20b}, -C(R^{20a})=N(R^{20a}), and -C(R^{20a})=N(OR^{20a}), wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^b;

R^{20a} in each occurrence is independently selected from the group consisting of H, C₁₋₆alkyl, carbocyclyl, and heterocyclyl, wherein said C₁₋₆alkyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^b;

R^{20b} in each occurrence is independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl, wherein said C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^b;

R³⁰ in each occurrence is independently selected from the group consisting of halo, -CN, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocyclyl, heterocyclyl, -OR^{30a}, -SR^{30a}, -N(R^{30a})₂, -N(R^{30a})C(O)R^{30b}, -N(R^{30a})N(R^{30a})₂, -NO₂, -C(O)H, -C(O)R^{30b}, -C(O)₂R^{30a}, -C(O)N(R^{30a})₂, -OC(O)N(R^{30a})₂, -N(R^{30a})C(O)₂R^{30a}, -N(R^{30a})C(O)N(R^{30a})₂, -OC(O)R^{30b},

$-\text{S}(\text{O})\text{R}^{30\text{b}}$, $-\text{S}(\text{O})_2\text{R}^{30\text{b}}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{30\text{a}})_2$, $-\text{N}(\text{R}^{30\text{a}})\text{S}(\text{O})_2\text{R}^{30\text{b}}$, $-\text{C}(\text{R}^{30\text{a}})=\text{N}(\text{R}^{30\text{a}})$, and $-\text{C}(\text{R}^{30\text{a}})=\text{N}(\text{OR}^{30\text{a}})$, wherein said $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^c ;

$\text{R}^{30\text{a}}$ in each occurrence is independently selected from the group consisting of H, $\text{C}_{1-6}\text{alkyl}$, carbocyclyl, and heterocyclyl, wherein said $\text{C}_{1-6}\text{alkyl}$, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^c ;

$\text{R}^{30\text{b}}$ in each occurrence is independently selected from the group consisting of $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, carbocyclyl, and heterocyclyl, wherein said $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^c ;

R^{40} in each occurrence is independently selected from the group consisting of halo, $-\text{CN}$, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, carbocyclyl, heterocyclyl, $-\text{OR}^{40\text{a}}$, $-\text{SR}^{40\text{a}}$, $-\text{N}(\text{R}^{40\text{a}})_2$, $-\text{N}(\text{R}^{40\text{a}})\text{C}(\text{O})\text{R}^{40\text{b}}$, $-\text{N}(\text{R}^{40\text{a}})\text{N}(\text{R}^{40\text{a}})_2$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})\text{R}^{40\text{b}}$, $-\text{C}(\text{O})_2\text{R}^{40\text{a}}$, $-\text{C}(\text{O})\text{N}(\text{R}^{40\text{a}})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{40\text{a}})_2$, $-\text{N}(\text{R}^{40\text{a}})\text{C}(\text{O})_2\text{R}^{40\text{a}}$, $-\text{N}(\text{R}^{40\text{a}})\text{C}(\text{O})\text{N}(\text{R}^{40\text{a}})_2$, $-\text{OC}(\text{O})\text{R}^{40\text{b}}$, $-\text{S}(\text{O})\text{R}^{40\text{b}}$, $-\text{S}(\text{O})_2\text{R}^{40\text{b}}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{40\text{a}})_2$, $-\text{N}(\text{R}^{40\text{a}})\text{S}(\text{O})_2\text{R}^{40\text{b}}$, $-\text{C}(\text{R}^{40\text{a}})=\text{N}(\text{R}^{40\text{a}})$, and $-\text{C}(\text{R}^{40\text{a}})=\text{N}(\text{OR}^{40\text{a}})$, wherein said $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^d ;

$\text{R}^{40\text{a}}$ in each occurrence is independently selected from the group consisting of H, $\text{C}_{1-6}\text{alkyl}$, carbocyclyl, and heterocyclyl, wherein said $\text{C}_{1-6}\text{alkyl}$, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^d ;

$\text{R}^{40\text{b}}$ in each occurrence is independently selected from the group consisting of $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, carbocyclyl, and heterocyclyl, wherein said $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^d ;

R^{50} in each occurrence is independently selected from the group consisting of halo, $-\text{CN}$, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, carbocyclyl, heterocyclyl, $-\text{OR}^{50\text{a}}$, $-\text{SR}^{50\text{a}}$, $-\text{N}(\text{R}^{50\text{a}})_2$, $-\text{N}(\text{R}^{50\text{a}})\text{C}(\text{O})\text{R}^{50\text{b}}$, $-\text{N}(\text{R}^{50\text{a}})\text{N}(\text{R}^{50\text{a}})_2$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})\text{R}^{50\text{b}}$, $-\text{C}(\text{O})_2\text{R}^{50\text{a}}$, $-\text{C}(\text{O})\text{N}(\text{R}^{50\text{a}})_2$, $-\text{OC}(\text{O})\text{N}(\text{R}^{50\text{a}})_2$, $-\text{N}(\text{R}^{50\text{a}})\text{C}(\text{O})_2\text{R}^{50\text{a}}$, $-\text{N}(\text{R}^{50\text{a}})\text{C}(\text{O})\text{N}(\text{R}^{50\text{a}})_2$, $-\text{OC}(\text{O})\text{R}^{50\text{b}}$, $-\text{S}(\text{O})\text{R}^{50\text{b}}$, $-\text{S}(\text{O})_2\text{R}^{50\text{b}}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{50\text{a}})_2$, $-\text{N}(\text{R}^{50\text{a}})\text{S}(\text{O})_2\text{R}^{50\text{b}}$, $-\text{C}(\text{R}^{50\text{a}})=\text{N}(\text{R}^{50\text{a}})$, and $-\text{C}(\text{R}^{50\text{a}})=\text{N}(\text{OR}^{50\text{a}})$, wherein said $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^e ;

R^{50a} in each occurrence is independently selected from the group consisting of H, C_{1-6} alkyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^e ;

R^{50b} in each occurrence is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^e ;

R^{60} in each occurrence is independently selected from the group consisting of halo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, heterocyclyl, $-OR^{60a}$, $-SR^{60a}$, $-N(R^{60a})_2$, $-N(R^{60a})C(O)R^{60b}$, $-N(R^{60a})N(R^{60a})_2$, $-NO_2$, $-C(O)H$, $-C(O)R^{60b}$, $-C(O)_2R^{60a}$, $-C(O)N(R^{60a})_2$, $-OC(O)N(R^{60a})_2$, $-N(R^{60a})C(O)_2R^{60a}$, $-N(R^{60a})C(O)N(R^{60a})_2$, $-OC(O)R^{60b}$, $-S(O)R^{60b}$, $-S(O)_2R^{60b}$, $-S(O)_2N(R^{60a})_2$, $-N(R^{60a})S(O)_2R^{60b}$, $-C(R^{60a})=N(R^{60a})$, and $-C(R^{60a})=N(OR^{60a})$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^f ;

R^{60a} in each occurrence is independently selected from the group consisting of H, C_{1-6} alkyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^f ;

R^{60b} in each occurrence is independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, and heterocyclyl are each independently and optionally substituted with one or more R^f ;

R^a , R^b , R^c , R^d , R^e , and R^f in each occurrence are independently selected from the group consisting of halo, -CN, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocyclyl, heterocyclyl, $-OR^m$, $-SR^m$, $-N(R^m)_2$, $-N(R^m)C(O)R^n$, $-N(R^m)N(R^m)_2$, $-NO_2$, $-C(O)H$, $-C(O)R^n$, $-C(O)_2R^m$, $-C(O)N(R^m)_2$, $-OC(O)N(R^m)_2$, $-N(R^m)C(O)_2R^m$, $-N(R^m)C(O)N(R^m)_2$, $-OC(O)R^n$, $-S(O)R^n$, $-S(O)_2R^n$, $-S(O)_2N(R^m)_2$, $-N(R^m)S(O)_2R^n$, $-C(R^m)=N(R^m)$, and $-C(R^m)=N(OR^m)$;

R^m in each occurrence is independently selected from the group consisting of H and C_{1-6} alkyl; and

R^n in each occurrence is C_{1-6} alkyl.

2. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 1, wherein
Ring A is 5-membered heteroaryl, wherein said 5-membered heteroaryl is optionally substituted on carbon with one or more R^1 ;
 R^1 in each occurrence is independently selected from C_{1-6} alkyl, $-OR^{1a}$, and saturated carbocyclyl; and
 R^{1a} is C_{1-6} alkyl.
3. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 and 2, wherein
Ring B is selected from phenyl and 6-membered heteroaryl, wherein said phenyl and 6-membered heteroaryl is optionally substituted with one or more R^6 ; and
 R^6 is halo.
4. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 3, wherein
 R^2 is selected from H and C_{1-6} alkyl.
5. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 4, wherein
 R^3 is selected from H and -CN.
6. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 5, wherein
 R^5 is C_{1-6} alkyl, wherein said C_{1-6} alkyl is optionally substituted with one more $-OR^{50}$; and
 R^{50} is C_{1-6} alkyl.
7. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 6, wherein **X** is selected from -NH- and -O-.

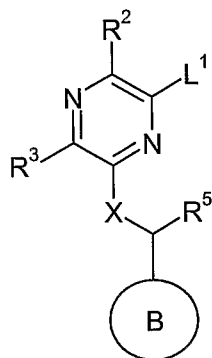
8. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein
Ring A is selected from 5-cyclopropyl-1*H*-pyrazol-3-yl, 5-methyl-1*H*-pyrazol-3-yl, 5-methoxy-1*H*-pyrazol-3-yl, 5-methyl-thiazol-2-yl, and 5-amino-2-cyano-1,3-thiazol-4-yl;
Ring B is selected from 3,5-difluorophenyl, 4-fluorophenyl, 5-fluoropyridin-2-yl, and 4-fluorophenylpyrimidin-2-yl;
X is selected from -NH- and -O-;
R² is selected from H and methyl;
R³ is selected from H and -CN; and
R⁵ is methyl.
9. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 8, for use as a medicament.
10. The use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 8, in the manufacture of a medicament for use in treating myeloproliferative disorders, myelodysplastic syndrome, and cancer, in a warm-blooded animal such as man.
11. The use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 8, in the manufacture of a medicament 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.
12. The use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 8, in the manufacture of a medicament for use in 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.

13. The use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 8, in the manufacture of a medicament for use in the production of an anti-proliferative effect, in a warm-blooded animal such as man.
14. The use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 8, in the manufacture of a medicament for use in the production of a JAK inhibitory effect.
15. The use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 8, in the manufacture of a medicament for use in the production of a TRK inhibitory effect.
16. The use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 8, in the manufacture of a medicament for use in the treatment of cancer.
17. 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, as claimed in any one of claims 1 to 8.
18. A method for treating myeloproliferative disorders, myelodysplastic syndrome, and cancers (solid and hematologic tumors), fibroproliferative and differentiative disorders,

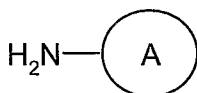
psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acromegaly, acute and chronic inflammation, bone diseases, and ocular diseases with retinal vessel proliferation, in a warm-blooded animal 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, as claimed in any one of claims 1 to 8.

19. A pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 8, and at least one pharmaceutically acceptable carrier, diluent, or excipient.
20. A process for preparing a compound of Formula (I) as claimed in any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, said process comprising reacting a pyrazine of Formula (A):



Formula (A)

with an amine of Formula (B):



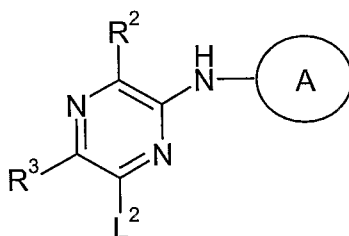
Formula (B)

and thereafter if appropriate:

- 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,

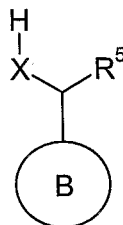
wherein L^1 is a leaving group.

21. A process for preparing a compound of Formula (I) as claimed in any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, said process comprising reacting a pyrazine of Formula (C):



Formula (C)

with a compound of Formula (D):



Formula (D);

and thereafter if appropriate:

- 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^2 is a leaving group.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB2008/001046

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/14 C07D403/12 C07D403/14 C07D417/14 A61K31/497
A61P35/00

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

B. FIELDS SEARCHED

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

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

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

EPO-Internal, WPI Data, BEILSTEIN Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2006/117560 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; SCOTT DAVID [US]; WANG H) 9 November 2006 (2006-11-09) page 1, line 10 - page 2, line 20 page 27 - page 29; examples 1-8 claim 1	1-21
Y	WO 2006/123113 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; WANG BIN [US]; WANG TAO) 23 November 2006 (2006-11-23) page 1, line 10 - page 2, line 20 page 35 - page 48; examples 1-38 claim 1	1-21

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

23 July 2008

Date of mailing of the international search report

04/08/2008

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INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2008/001046

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/103010 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; LYNE PAUL [US]; WANG BIN) 3 November 2005 (2005-11-03) cited in the application page 1, line 10 - page 2, line 19 page 29 - page 36; examples 1-28 claim 1	1-21
Y	WO 2006/082392 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; DAVIES AUDREY [US]; LAMB) 10 August 2006 (2006-08-10) page 1, line 10 - page 2, line 19 page 48 - page 94; examples 1-134 claim 1	1-21
Y	US 2003/022885 A1 (BEBBINGTON DAVID [GB] ET AL) 30 January 2003 (2003-01-30) page 1, paragraph 3 - page 2, paragraph 13 Examples tables 1-3 claim 1	1-21
Y	US 2004/009981 A1 (BEBBINGTON DAVID [GB] ET AL) 15 January 2004 (2004-01-15) page 1, paragraph 3 - page 2, paragraph 19 Examples tables 1-4 claim 1	1-21
Y	WO 03/077921 A (VERTEX PHARMA [US]; BEBBINGTON DAVID [GB]; BINCH HAYLEY [GB]; CHARRIER) 25 September 2003 (2003-09-25) page 1, paragraph 3 - page 5, paragraph 19 page 22 - page 37; examples iia-1-ivb-3; tables 1-4	1-21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2008/001046

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

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

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

Although claims 17-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2008/001046

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