Title: PYRIDYL SUBSTITUTED PYRIMIDINE DERIVATIVES

Abstract: The present invention relates to pyridyl substituted pyrimidine compounds that are useful as agents for the treatment of kinase related disorders such as proliferative disorders. More particularly, the present invention relates to oxygen linked and pyridyl substituted pyrimidine compounds, methods for their preparation, pharmaceutical compositions containing these compounds and uses of these compounds in the treatment of proliferative disorders. These compounds may be useful as medicaments for the treatment of a number of kinase related disorders such as proliferative disorders including tumours and cancers as well as other disorders or conditions related to or associated with kinases.
FIELD OF THE INVENTION

The present invention relates to pyrimidine compounds that may be useful as agents for targeting kinase related disorders. More particularly, the present invention relates to pyridyl substituted pyrimidine compounds, methods for their preparation, pharmaceutical compositions containing these compounds and uses of these compounds in the treatment of kinase related disorders such as proliferative disorders. These compounds may therefore be useful as medicaments for the treatment of a number of kinase related disorders such as proliferative disorders including tumours and cancers as well as other conditions or disorders associated with kinases.

BACKGROUND OF THE INVENTION

There are a number of kinase related disorders known at the present time with proliferative disorders being one of the best characterised. Proliferative disorders such as cancer are characterised by the uncontrolled growth of cells within the body. As such proliferative disorders generally involve an abnormality in the control of cell growth and/or division leading to the formation of tumour and ultimately death. Without wishing to be bound by theory it is thought that this is caused by the pathways that regulate cell growth and division being altered in cancer cells. The alteration is such that the effects of these normal regulatory mechanisms in controlling cell growth and division either fails or is bypassed.

The uncontrolled cell growth and/or division ultimately proves fatal for the patient as successive rounds of mutations on the part of the cell then typically lead to the cancer cells having a selective advantage over normal healthy cells in the body of the patient leading to the cancer cells predominating in the cell mass of the patient. The cancer cells then typically metastasize to colonize other tissues or parts of the body other than the part of origin of the cancer cell leading to secondary tumours. These secondary tumours eventually lead to organ failure and the death of the patient. It is the difficulty in controlling the rapid cell growth and division that is characteristic of cancer cells that make it hard to come up with effective chemotherapeutic strategies.

A number of traditional treatments for proliferative disorders such as cancer seek to take advantage of their higher proliferative capacity and thus their higher sensitivity to DNA damage. Treatments that have been utilised include ionizing radiation (γ-rays,
X-rays and the like) as well as cytotoxic agents such as bleomycin, cis-platin, vinblastine, cyclophosphamide, 5'-fluorouracil and methotrexate. These treatments all rely on causing damage to DNA and destabilisation of the chromosomal structure eventually leading to death of the cancer cells.

A difficulty with many of these approaches is that they are non-selective for cancer cells and healthy cells can and often will be adversely affected by the treatment. This is hardly surprising given that the cellular mechanisms targeted by these strategies occur in healthy cells as well as in cancer cells (although typically at slower rates in the healthy cells) and this highlights the difficulty in achieving successful treatment of the cancer in the patient without causing irreparable harm to the healthy cells. As such with many of these treatments there can be devastating side effects which can not only significantly reduce the short term quality of life of the patient but may also have long term detriments on the health of the patient should they survive the cancer attack.

Whilst some of the above problems have substantially been overcome by the development of selective anti-cancer agents (such as tamoxifen) the effectiveness of all chemotherapeutic agents is subject to the development of drug resistance by the cancer cells in the patient. The development of drug resistance in the cancer cells of a patient tends to be class specific and therefore if the cancer cells of a patient develop drug resistance to a class of anti-cancer drugs then all compounds within that class are typically rendered ineffective in the further treatment of that patient. As such in improving clinical outcomes for patients the identification of alternative chemotherapeutic agents are essential in providing the oncologist with an arsenal of drugs that may be used in any given situation.

The development of different classes of therapeutic agents is therefore important as it can help avoid the development of drug resistance and can also be used in combination therapies. Such combination therapies typically involve the use of anti-cancer drugs with different properties and cellular targets which in turn tends to increase the overall effectiveness of any chosen chemotherapy regime and limits the possibility of drug resistance developing in the patient.

One of the major advances in cancer research has been the clinical validation of molecularly targeted drugs that inhibit the activity of protein kinases. Small-molecule kinase inhibitors that are now approved for oncology indications include imatinib, gefitinib,
erlotinib, sorafenib, sunitinib and dasatinib [Baselga J., Science, 2006, 312, 1175-1178]. A number of kinases such as JAK2, FLT3 and CDK2 are promising kinase targets for pharmacological intervention in solid tumours, hematological malignancies, myeloproliferative disorders and non-malignant proliferative disorders like keloids.

The Janus kinases (JAK) are a family of cytoplasmic tyrosine kinases consisting of JAK1, JAK2, JAK3 and Tyk2. They play a pivotal role in the signaling pathways of numerous cytokines, hormones and growth factors [Rawlings JS et al, J. Cell ScL, 2004, 117, 1281-1283]. Their intracellular substrates include the family of proteins called Signal Transducer and Activator of Transcription (STAT). The JAK-STAT pathways, through the proper actions of the ligands, regulate important physiological processes such as immune response to viruses, erythropoiesis, lactation, lipid homeostasis, etc. However, dysfunctional signaling caused by a myriad of factors result in pathophysiological conditions such as allergies, asthma, rheumatoid arthritis, severe combined immune deficiency, hematological malignancies, etc. In particular, mutations in JAK2 have been associated with myeloproliferative disorders (including polycythemia vera, essential thrombocythemia and idiopathic myelofibrosis) and a wide range of leukemias and lymphomas [Percy MJ et al, Hematol. Oncol., 2005, 23, 91-93]. Importantly, the myeloproliferative disorders belong to an area of unmet medical need where some treatment modalities have not been updated over the past few decades [Schafer Al, Blood, 2006, 107, 4214-4222].

The myeloproliferative disorders (MPDs) belong to a group of haematological malignancies arising from clonal expansion of mutated progenitor stem cells in the bone marrow. The association of one MPD, chronic myeloid leukaemia, with the Philadelphia chromosome has been well documented. The Philadelphia negative MPDs include Essential Thrombocythemia (ET), Polycythemia Vera (PV) and Chronic Idiopathic Myelofibrosis (MF). No effective treatment is currently available. The recent discovery that a single acquired somatic mutation in JAK2 appears responsible for many of the features of these MPDs promises to impact the diagnosis and treatment of patients with these disorders and to spur additional research into the origins of dysregulated cell growth and function. Until recently, most MPDs have been considered to be rare or orphan diseases but studies underway suggest a much higher prevalence.

Essential Thrombocythemia is a chronic MPD characterized by an increased number of circulating platelets, profound marrow megakaryocyte hyperplasia,
spleenomegaly and a clinical course punctuated by hemorrhagic or thrombotic episodes or both. Current treatment options include low dose aspirin, or platelet lowering agents such as anagrelide, interferon or hydroxyurea. These treatments have severe side effects that compromise the quality of life of patients.

Polycythemia Vera is a chronic progressive MPD characterized by an elevated hematocrit, an increase in the red cell mass, and usually by an elevated leukocyte count, an elevated platelet count and an enlarged spleen. The most common cause of morbidity and mortality is the predisposition of PV patients to develop life threatening arterial and venous thromboses. Treatment options include: phlebotomy with low dose aspirin or myelosuppressive therapy options such as hydroxyurea, interferon or anagrelide. Again, these treatments are not ideal due to severe side effects.

Chronic Idiopathic Myelofibrosis (MF) is a chronic malignant hematological disorder characterized by an enlarged spleen, varying degrees of anemia and low platelet counts, red cells in the peripheral blood that resemble tear drops, the appearance of small numbers of immature nucleated red cells and white cells in the blood, varying degrees of fibrosis of the marrow cavity (myelofibrosis) and the presence of marrow cells outside the marrow cavity (extramedullar/ hematopoiesis or myeloid metaplasia). Current treatment is directed at alleviation of constitutional symptoms, anemia and symptomatic splenomegaly. Treatment options include hydroxyurea, interferon, thalidomide with prednisone, and allogeneic stem cell transplant. MF has the worst prognosis among the Philadelphia negative MPD and represents an area of greatest unmet medical need.

In addition, due to its role in the angiotensin II signaling pathway, JAK2 is also implicated in the etiology of cardiovascular diseases like congestive heart failure and pulmonary hypertension [Berk BC et al, Circ. Res, 1997, 80, 607-616]. Furthermore, a putative role for JAK2 has been demonstrated in keloid pathogenesis and may constitute a new approach for keloid management [Lim CP et al, Oncogene, 2006, 25, 5416-5425]. Yet another potential application for JAK2 inhibitors lies in the treatment of retinal diseases as JAK2 inhibition was found to offer protective effects on photoreceptors in a mouse model of retinal degeneration [Samardzija M et al, FASEB J., 2006, 10, 1096].

A family of Class II receptor tyrosine kinases (RTK), including c-Fms, c-Kit, fms-like receptor tyrosine kinase 3 (FLT3), and platelet-derived growth factor receptors (PDGFRα and β), play an important role in the maintenance, growth and development of
hematopoietic and non-hematopoietic cells. Over expression and activating mutations of these RTKs are known to be involved in the pathophysiology of diverse human cancers from both solid and hematological origins [Hannah AL, Curr. Mol. Med., 2005, 5, 625-642]. FLT3 mutations were first reported as internal tandem duplication (FLT3/ITD) of the juxtamembrane domain-coding sequence; subsequently, point mutations, deletions, and insertions surrounding the D835 coding sequence have been found [Parcells BW et al, Stem Cells, 2006, 24, 1174-1184]. FLT3 mutations are the most frequent genetic alterations reported in acute myeloid leukemia (AML) and are involved in the signaling pathway of autonomous proliferation and differentiation block in leukemia cells [Tickenbrook L et al, Expert Opin. Emerging Drugs, 2006, 11, 1-13]. Several clinical studies have confirmed that FLT3/ITD is strongly associated with a poor prognosis. Because high-dose chemotherapy and stem cell transplantation cannot overcome the adverse effects of FLT3 mutations, the development of FLT3 kinase inhibitors could produce a more efficacious therapeutic strategy for leukemia therapy.

Cyclin-dependent kinases (CDKs) are serine-threonine kinases that play important roles in cell cycle control (CDK1, 2, 4 and 6), transcription initiation (CDK7 and 9), and neuronal function (CDK5) [Knockaert M et al, Trends Pharmacol. Sci, 2002, 23, 417-425]. Aberrations in the cell cycle CDKs and their cyclin partners have been observed in various tumor types, including those of the breast, colon, liver and brain [Shapiro GI, J. Clin. Oncol., 2006, 24, 1770-1783]. It is believed that the pharmacological inhibition of CDK1, 2, 4, 6 and/or 9 may provide a new therapeutic option for diverse cancer patients. In particular, the simultaneous inhibition of CDK1, 2 and 9 has recently been shown to result in enhanced apoptotic killing of lung cancer (H1299) and osteosarcoma cells (U2OS), compared with inhibition of single CDK alone [Cai D et al, Cancer Res, 2006, 66, 9270-9280].

Recent advances in biomedical research, including major breakthroughs such as genome-wide association studies, have uncovered new molecular pathways that may be pivotal in the initiation and progression of autoimmune and other inflammatory diseases. These discoveries provide a conceptual framework for the relentless efforts to search for better therapeutic modalities to treat these ailments. The signalling pathway involving JAKs (Janus kinases) and STATs (signal transducer and activator of transcription) is emerging as an important target for anti-autoimmune and anti-inflammatory drug discovery as it constitutes a pivotal signalling mechanism for many novel inflammatory cytokines. JAK2 for example is involved in numerous interleukin signaling pathways which may

Inflammation, for example, is a natural biological response to microbial challenge and other forms of threats or breach of tissue integrity. It is characterized by increased vascular permeability accompanied by an infiltration of specialized blood cells (neutrophils, macrophages, lymphocytes and plasma cells) into the inflamed area. These cellular responses are mediated by the appearance of adhesion molecules on endothelia and the release of inflammatory mediators (cytokines and prostaglandins) from tissue cells and leukocytes. The cardinal signs of inflammation are pain, edema, redness and warmth at the affected site. When occurring in a self-limiting fashion within the context of *bona fide* foreign insults, inflammation is a physiological process that puts the tissues on the path to recovery and prevents further damage.

Many pathological conditions in humans, however, involve inflammatory processes that were inadvertently dys-regulated and exaggerated. This can lead to chronic pain, severe morbidity, or even fatal consequences. Symptoms of inflammation are often present in many autoimmune diseases, which are pathological states caused by the body producing an inappropriate immune response against its own tissues. In such cases, the immune system ceases to recognize one or more of the body's normal constituents as "self" and generates auto-antibodies - antibodies that attack its own cells, tissues, and/or organs. This results in inflammation and other concomitant damage which together constitute the symptoms of autoimmune diseases.

The exact cause of autoimmune diseases, as to why normal cellular components or products become auto-antigens that elicit robust immunologic reactions, is unknown. There appears to be a genetic basis underlying susceptibility to many autoimmune conditions and the initiating role played by microbial infections is strong in other cases. Autoimmune disorders fall into two general types: those that affect many organs (systemic) and those where only a single organ or tissue is directly damaged by the autoimmune process (localized). However, the distinction becomes blurred as the effect of localized autoimmune disorders frequently extends beyond the targeted tissues, indirectly affecting other organs and systems.

A number of traditional treatments for autoimmune and other inflammatory diseases, such as corticosteroids, azathioprine, methotrexate, cyclosporine A, rely on the
potent non-specific immunosuppressive effects of these agents to mitigate the disease symptoms. These treatments are not satisfactory due to the side effects that will compromise the health of the patients over the long term, such as dysfunctional glucose homeostasis, osteoporosis, susceptibility to opportunistic infections, etc. While some of the above problems have been overcome by the development of new biological therapies (such as TNF-α blockers), about 30% of patients are not responsive to these new agents. As such, there is a need to provide further therapeutic options that would enable the autoimmune specialists to customise treatments for the individual patients. Following the identification of the potential importance of JAK kinases in mediating signalling in these conditions kinase inhibitors provide a potential source of therapeutics for these conditions.

There are therefore a number of kinase targets that have been identified as being involved in a number of disorders and compounds that target these kinases should display interesting biological activity. As such, compounds that are kinase inhibitors have the potential to meet the need to provide further biologically active compounds that would be expected to have useful, improved pharmaceutical properties in the treatment of kinase related conditions or disorders such as cancer and other proliferative disorders.

As a result of this need a number of compounds that are kinase inhibitors have been developed with varying levels of success for a number of reasons. It is desirable, for instance that the compounds developed be able to provide activity against more than one kinase as in many instances multi-faceted activity allows the compound to attack the disorder in a number of different ways/pathways. For example it is desirable that the compound display JAK2 activity as this kinase is associated with a number of disorders as discussed above. In addition it is desirable that the compound be a CDK inhibitor as cyclin dependent kinases are also found to be involved in a number of disorders.

Another issue that is often associated with molecules of this type that are developed as kinase inhibitors is that whilst many of them show good activity in vitro they do not have good "drug-like" properties and therefore are not suitable for clinical use. For example many compounds display poor solubility and/or high levels of protein binding both of which lead to the compound not being bio-available and, in addition, allows the compound to penetrate the brain typically leading to an increased chance of side effects in the central nervous system being observed. As such it is clearly desirable to provide kinase inhibitors that show desirable drug like properties.
Accordingly there is an ongoing need to develop further and improved kinase inhibitors that meet one or more of the above needs associated with kinase inhibitors present in the prior art.

The present applicants have identified a family of pyridyl substituted pyrimidines which show activity against JAK2 as well as being inhibitors of cyclin dependent kinases (such as CDK2) and have promising drug like properties. The compounds are thus very promising candidates for the treatment of kinase related conditions.

**SUMMARY OF THE INVENTION**

In one aspect the present invention provides a compound of formula (I):

![Formula (I)](attachment://formula.png)

wherein:

- R\(^1\) is selected from the group consisting of: H, halogen, OH, OCH\(_3\), OCF\(_3\), OCH\(_2\)CH\(_3\), NO\(_2\), NH\(_2\), NHCH\(_3\), NHCH\(_2\)CH\(_3\), N(CH\(_3\))\(_2\), SH, SCH\(_3\), optionally substituted C\(_1-4\)alkoxy, and optionally substituted C\(_r>C_4\)alkyl;

- each R\(^2\) is independently selected from the group consisting of H, halogen, OH, NO\(_2\), CN, NH\(_2\), optionally substituted C\(_r>C_2\)alkyl, optionally substituted C\(_2>C_1\)alkenyl, optionally substituted C\(_2>C_2\)alkynyl, optionally substituted C\(_3>C_1\)cycloalkyl, optionally substituted C\(_1>C_1\)heterocycloalkyl, optionally substituted d-C\(^n\)alkoxy, optionally substituted C\(_r>C_1\)heteroalkoxy, optionally substituted C\(_r>C_1\)alkylamino, SR\(^4\), SO\(_3\)H, SO\(_2\)NH\(_2\), SO\(_2\)R\(^4\), SONH\(_2\), SOR\(^4\), COR\(^4\), COOH, COOR\(^4\), CONHR\(^4\), NHCOR\(^4\), NHOOR\(^4\), NHO\(_2\)R\(^4\), NHCONHR\(^4\), NR\(^4\)R\(^5\), and acyl;
each R³ is independently selected from the group consisting of H, halogen, OH, NO₂, CN, NH₂, optionally substituted C₃-C₁₂ alkyl, optionally substituted C₂-C₁₂ alkenyl, optionally substituted C₂-C₁₂ alkynyl, optionally substituted d-C₁₀ heteroalkyl, optionally substituted C₃-C₁₂ cycloalkyl, optionally substituted C₃-C₁₂ cycloalkenyl, optionally substituted C₁-C₁₂ heterocycloalkyl, optionally substituted C₁-C₁₂ heterocycloalkenyl, optionally substituted C₅-C₁₀aryl, optionally substituted C₅-C₁₀ heteroaryl, optionally substituted d-C₅ heteroaryl, optionally substituted d-C₅ heterocycloalkoxy, optionally substituted C₂-C₁₂ alkenyloxy, optionally substituted C₂-C₁₂ alkynylloxy, optionally substituted C₁-C₁₂ heterocycloalkoxy, optionally substituted C₁-C₁₂ heterocycloalkenyloxy, optionally substituted C₆-C₁₀ aryl, optionally substituted CrC₅ heteroaryloxy, optionally substituted d-dzalkylamino, SR⁴, SO₃H, SO₂NH₂, SO₂R⁴, SONH₂, SOR⁴, COR⁴, COOH, COOR⁴, CONHR⁴, NHCOR⁴, NHCOR⁴, NHCOOR⁴, NHSO₂R⁴, NHCONHR⁴, NR⁴R⁵, and acyl;

each R⁴ and R⁵ is independently selected from the group consisting of H, optionally substituted Cl-C₁₂ alkyl, optionally substituted C₂-C₁₂ alkenyl, optionally substituted C₂-C₁₂ alkynyl, optionally substituted CrC₁₀ heteroalkyl, optionally substituted C₃-C₁₀ cycloalkyl, optionally substituted C₃-C₁₀ cycloalkenyl, optionally substituted C₁-C₁₀ heterocycloalkyl, optionally substituted CrC₁₂ heterocycloalkenyl, optionally substituted C₆-C₁₀ aryl, and optionally substituted Cl-C₁₀ heteroaryl;

m is an integer selected from the group consisting of 0, 1, 2, and 3;

n is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

L is a group of formula:

\[-X¹-Y-X²⁻\]

wherein X¹ is attached to the pyridyl moiety and X² is attached to the phenyl moiety, and wherein X¹, X² and Y are selected such that the group L has between 5 and 15 atoms in the normal chain,

X¹ and X² are each independently a heteroalkyl group containing at least one oxygen atom in the normal chain,

Y is a group of formula -CRᵃ⁻CRᵇ⁻ or an optionally substituted cycloalkyl group,
wherein \( \text{R}^a \) and \( \text{R}^b \) are each independently selected from the group consisting of 
H, and optionally substituted CrC^alkyl,
or a pharmaceutically acceptable salt, N-oxide, or prodrug thereof.

As with any group of structurally related compounds which possess a particular utility, certain embodiments of variables of the compounds of the Formula (I), are particularly useful in their end use application.

In the compounds of the invention \( \text{X}^1 \), \( \text{X}^2 \) and \( \text{Y} \) are chosen such that there are between 5 and 15 atoms in the normal chain. In one embodiment of the compounds of the invention \( \text{X}^1 \), \( \text{X}^2 \) and \( \text{Y} \) are chosen such that there are between 6 and 15 atoms in the normal chain. In one specific embodiment of the compounds of the invention \( \text{X}^1 \), \( \text{X}^2 \) and \( \text{Y} \) are chosen such that there are 7 atoms in the normal chain. In another specific embodiment of the compounds of the invention \( \text{X}^1 \), \( \text{X}^2 \) and \( \text{Y} \) are chosen such that there are 8 atoms in the normal chain.

In the compounds of the invention \( \text{X}^1 \) and \( \text{X}^2 \) are each independently a heteroalkyl group containing at least one oxygen atom in the normal chain.

In certain embodiments \( \text{X}^1 \) is selected from the group consisting of:

(a) \(-\text{OC}_{1-5}\text{-alkyl}-\),
(b) \(-\text{CvsalkylO-}, \text{ and}
(c) \(-\text{d-salkylOC'salkyl}-.\)

In certain embodiments \( \text{X}^1 \) is selected from the group consisting of:

(a) \(-\text{OCH}_2^1\),
(b) \(-\text{CH}_2\text{O-},\)
(c) \(-\text{OCH}_2^1\text{CH}_2^2\),
(d) \(-\text{CH}_2\text{CH}_2\text{O-},\)
(e) \(-\text{CH}_2\text{OCH}_2^1\), \text{ and}
(f) \(-\text{CH}_2\text{CH}_2\text{OCH}_2^1-.\)

In one specific embodiment \( \text{X}^1 \) is \(-\text{OCH}_2^1\). In another specific embodiment \( \text{X}^1 \) is \(-\text{CH}_2\text{O-}. \) In another specific embodiment \( \text{X}^1 \) is \(-\text{OCH}_2^1\text{CH}_2^2-. \) In another specific
embodiment \( \text{X}^1 \) is \(-\text{CH}_2\text{CH}_2\text{O}^-\). In another specific embodiment \( \text{X}^1 \) is \(-\text{CH}_2\text{OCH}_2^-\). In another specific embodiment \( \text{X}^1 \) is \(-\text{CH}_2\text{CH}_2\text{OCH}_2^-\).

In certain embodiments \( \text{X}^2 \) is selected from the group consisting of:

(a) \(-\text{OC}_{1-5}\text{alkyl}^-\),
(b) \(-\text{C}_{1-5}\text{alkylO}^-\), and
(c) \(-\text{C}_{1-5}\text{alkylOC}_{1-5}\text{alkyl}^-\).

In certain embodiments \( \text{X}^2 \) is selected from the group consisting of:

(a) \(-\text{OCH}_2^-\),
(b) \(-\text{CH}_2\text{O}^-\),
(c) \(-\text{OCH}_2\text{CH}_2^-\),
(d) \(-\text{CH}_2\text{CH}_2\text{O}^-\),
(e) \(-\text{CH}_2\text{OCH}_2^-\), and
(f) \(-\text{CH}_2\text{CH}_2\text{OCH}_2^-\).

In one specific embodiment \( \text{X}^2 \) is \(-\text{OCH}_2^-\). In another specific embodiment \( \text{X}^1 \) is \(-\text{CH}_2\text{O}^-\). In another specific embodiment \( \text{X}^2 \) is \(-\text{OCH}_2\text{CH}_2^-\). In another specific embodiment \( \text{X}^2 \) is \(-\text{CH}_2\text{CH}_2\text{O}^-\). In another specific embodiment \( \text{X}^2 \) is \(-\text{CH}_2\text{OCH}_2^-\). In another specific embodiment \( \text{X}^2 \) is \(-\text{CH}_2\text{CH}_2\text{OCH}_2^-\).

In one specific embodiment \( \text{X}^1 \) is \(-\text{OCH}_2\text{CH}_2^-\) and \( \text{X}^2 \) is \(-\text{CH}_2\text{OCH}_2^-\). This provides compounds of formula (Ia).

![Diagram](image-url)  

Formula (Ia)

wherein \( R^1, R^2, R^3, Y, m, \) and \( n \) are as defined above, or a pharmaceutically acceptable salt, N-oxide, or prodrug thereof.
In one embodiment Y is selected from the group consisting of:

\[
\begin{align*}
\text{X} & \quad \text{X} \\
\end{align*}
\]

and

In a specific embodiment Y is

\[
\begin{align*}
\text{X} & \quad \text{X} \\
\end{align*}
\]

In another specific embodiment Y is

\[
\begin{align*}
\end{align*}
\]

In another specific embodiment Y is a cyclopropyl group.

In one specific embodiment \(X^1\) is \(-\text{OCH}_2\text{CH}_2^-\) and \(X^2\) is \(-\text{CH}_2\text{OCH}_2^-\) and Y is

\[
\begin{align*}
\text{X} & \quad \text{X} \\
\end{align*}
\]

This provides compounds of formula (Ib).
Formula (Ib)

wherein $R_1$, $R_2$, $R_3$, $m$, and $n$ are as defined above, or a pharmaceutically acceptable salt, N-oxide, or prodrug thereof.

In certain embodiments $R_1$ is selected from the group consisting of $H$, $Cl$, $F$, methyl, and methoxy. In one specific embodiment $R_1$ is $H$. In another specific embodiment $R_1$ is $Cl$. In one specific embodiment $R_1$ is $F$. In another specific embodiment $R_1$ is methyl. In another specific embodiment $R_1$ is methoxy.

In certain embodiments $R_2$ is selected from the group consisting of $H$, chloro, bromo, iodo, methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, phenyl, hydroxy, methoxy, ethoxy, phenoxy, benzyloxy, amino, methylamino, ethylamino, propylamino, butylamino, pentylamino and hexylamino, each of which may be optionally substituted.

In certain embodiments $R_2$ is selected from the group consisting of $H$, chloro, bromo, iodo, amino, methylamino, ethylamino, propylamino, butylamino, pentylamino and hexylamino, each of which may be optionally substituted.

In certain embodiments $R_2$ is $H$.

In certain embodiments $n$ is 0.
In certain embodiments n is 1.

In certain embodiments each \( R^3 \) is independently selected from the group consisting of halogen, \( \text{OH}, \text{NO}_2 \), cyano, \( \text{NH}_2 \), optionally substituted \( \text{Cl}-\text{C}_{12} \text{alkyl} \), optionally substituted \( \text{C}_r \text{C}_{10} \text{heteroalkyl} \), optionally substituted \( \text{CrC}^\text{alkyloxy} \), \( \text{SR}^3 \), \( \text{SO}_3\text{H} \), \( \text{SO}_3\text{NH}_2 \), \( \text{SO}_3\text{R}^3 \), \( \text{SONH}_2 \), \( \text{SOR}^3 \), \( \text{COR}^4 \), \( \text{COOH} \), \( \text{COOR}^3 \), \( \text{CONHR}^3 \), \( \text{NHCOOR}^3 \), \( \text{NHSO}_3\text{R}^3 \), \( \text{NHCONHR}^3 \), \( \text{NR}^3\text{R}^4 \), and acyl.

In certain embodiments each \( R^3 \) is independently selected from the group consisting of optionally substituted \( \text{Cl}-\text{Ci}_0 \text{heteroalkyl} \), optionally substituted \( \text{CrCi}_2 \text{heterocycloalkyl} \), and optionally substituted \( \text{C}_r \text{C}_{12} \text{alkyloxy} \).

In certain embodiments each \( R^3 \) is an optionally substituted \( \text{d-C}_{12} \text{alkyloxy} \) of the formula:

\[
\begin{align*}
\begin{array}{c}
A \\
\end{array}
\begin{array}{c}
B \\
\end{array}
\begin{array}{c}
P \\
\end{array}
\begin{array}{c}
D \\
\end{array}
\begin{array}{c}
R^{10} \\
\end{array}
\begin{array}{c}
R^{11} \\
\end{array}
\end{align*}
\]

wherein

\( A \) is selected from the group consisting of a bond, \( \text{O} \) and \( \text{CH}_2 \);

\( B \) is selected from the group consisting of \( \text{O} \) and \( \text{CH}_2 \);

with the proviso that only one of \( A \) and \( B \) is \( \text{O} \);

\( D \) is selected from the group consisting of \( \text{N} \) and \( \text{CR}^{12} \);

\( p \) is an integer selected from the group consisting of 0, 1, 2, 3, 4, 5, and 6;

\( R^{10} \) and \( R^{11} \) are independently selected from the group consisting of \( \text{H} \), optionally substituted \( \text{C}_1-\text{C}_{12} \text{alkyl} \), optionally substituted \( \text{C}_2-\text{C}_{12} \text{alkenyl} \), optionally substituted \( \text{C}_2-\text{C}_{12} \text{alkynyl} \), optionally substituted \( \text{C}_1-\text{C}_{10} \text{heteroalkyl} \), optionally substituted \( \text{C}_3-\text{C}_{12} \text{cycloalkyl} \), optionally substituted \( \text{C}_3-\text{C}_{12} \text{cycloalkenyl} \), optionally substituted \( \text{C}_1-\text{C}_{12} \text{heterocycloalkyl} \),
optionally substituted \( \text{C}_1^1 \text{C}_1^2 \) heterocycloalkenyl, optionally substituted \( \text{C}_6^1 \text{C}_{18}^8 \) aryl, and optionally substituted \( \text{C}^\text{heteroaryl} \), or

\[ \text{R}^{10} \text{ and } \text{R}^{11} \text{ when taken together with the atom to which they are attached form an} \]

optionally substituted cyclic moiety;

\[ \text{R}^{12} \text{ is H or optionally substituted } \text{C}_1^1 \text{C}_6^1 \text{ alkyl.} \]

In one specific embodiment A is \( \text{CH}_2^2 \). In one specific embodiment A is O.

In one specific embodiment B is O. In one specific embodiment B is \( \text{CH}_2^2 \).

In one specific embodiment A is O and B is \( \text{CH}_2^2 \).

In this embodiment p is an integer selected from the group consisting of 0, 1, 2, 3, 4, 5, and 6. In one specific embodiment p is 0. In one specific embodiment p is 1. In one specific embodiment p is 2. In one specific embodiment p is 3. In one specific embodiment p is 4. In one specific embodiment p is 5. In one specific embodiment p is 6.

In one form of this embodiment D is N.

In one form of this embodiment D is CH.

In one form of this embodiment \( \text{R}^{10} \) and \( \text{R}^{11} \) when taken together form an optionally substituted cyclic moiety. The optionally substituted cyclic moiety may be any suitable cyclic moiety including a \( \text{C}_1^1 \text{C}_{10}^9 \) cycloalkyl or a \( \text{C}_1^1 \text{C}_{10}^9 \) heterocycloalkyl moiety.

In one form of the invention D is N and \( \text{R}^{10} \) and \( \text{R}^{11} \) when taken together with the nitrogen atom to which they are attached form an optionally substituted piperidinyl moiety.

In one specific embodiment \( \text{R}^{10} \) and \( \text{R}^{11} \) when taken together with the nitrogen atom to which they are attached form 4-methyl-piperidin-1-yl. In one specific embodiment \( \text{R}^{10} \) and \( \text{R}^{11} \) when taken together with the nitrogen atom to which they are attached form a pyrrolidinyl moiety.

In one specific embodiment \( \text{R}^{3} \) is:
In certain embodiments each $R^3$ is independently selected from the group consisting of:
In certain embodiments R⁴ is selected from the group consisting of H and C₁–C₄ alkyl. In a specific embodiment R⁴ is C₁–C₄ alkyl. In another specific embodiment R⁴ is H.

In certain embodiments R⁵ is selected from the group consisting of C₁–C₄ alkyl, heteroalkyl and acyl. In a specific embodiment R⁵ is C₁–C₄ alkyl. In another specific embodiment R⁵ is H.

Many if not all of the variables discussed above may be optionally substituted. If the variable is optionally substituted then in certain embodiments the optional substituent is selected from the group consisting of: halogen, =0, =S, CN, NO₂, CF₃, OCF₃, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkoxyheteroaryl, alkenyloxy, alknyloxy, cycloalkyloxy, cycloalkenyloxy, heterocycloalkyloxy, heterocycloalkenyloxy, aryloxy, heteroaryloxy,
arylalkyl, heteroarylalkyl, arylalkyloxy, amino, alkylamino, acylamino, aminoalkyl, ary lamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, aminoalkyl, alkoxyalkyl, COOH, COR\(^6\), C(O)OR\(^6\), SO\(_2\)R\(^6\), SH, SR\(^6\), OR\(^6\) and acyl, each of which may be optionally substituted, and

\[ R^6 \text{ is } H, \text{ optionally substituted } d-C^\text{alkyl}, \text{ optionally substituted } C_2^\text{-}C_{12} \text{ alkenyl, } \\
\text{ optionally substituted } C_2^\text{-}C_{12} \text{ alkenyl, } \text{ optionally substituted } C_1^\text{-}C_{10} \text{ heteroalkyl, } \\
\text{ optionally substituted } C_3^\text{-}C_{12} \text{ cycloalkyl, } \text{ optionally substituted } C_{2}^\text{-}C_{2} \text{ cycloalkenyl, } \\
\text{ optionally substituted } C_1^\text{-}C_{12} \text{ heterocycloalkyl, } \text{ optionally substituted } C_1^\text{-}C_{12} \text{ heterocycloalkenyl, } \\
\text{ optionally substituted } C_6^\text{-}C_{18} \text{ aryl, } \text{ optionally substituted } Cr^\text{deheteroaryl, } \text{ and acyl.} \]

In certain embodiments the substituents are selected from the group consisting of: halogen, =O, =S, -CN, -NO\(_2\), alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, hydroxy, hydroxyalkyl, alkoxy, alkylamino, aminoalkyl, acylamino, phenoxy, alkoxyalkyl, benzyl, benzylsulfonyl, aromatic, aminosulfonyl, -C(O)OR\(^6\), COOH, SO\(_2\)R\(^6\), SH, and acyl.

In addition to compounds of Formula (I), the embodiments disclosed are also directed to pharmaceutically acceptable salts, pharmaceutically acceptable \text{N-oxides,}

pharmaceutically acceptable prodrugs, and pharmaceutically active metabolites of such compounds, and pharmaceutically acceptable salts of such metabolites.

The invention also relates to pharmaceutical compositions including a compound of the invention with a pharmaceutically acceptable carrier, diluent or excipient.

In a further aspect the invention provides a method of inhibiting one or more protein kinase(s) including exposing the one or more protein kinase(s) and/or co-factor(s) thereof to an effective amount of a compound of the invention.

The compounds disclosed herein may act directly and solely on the kinase molecule to inhibit biological activity. However, it is understood that the compounds may also act at least partially on co-factors that are involved in the phosphorylation process. For example, where the kinase is cyclin-dependent, a co-factor such as cyclin A is involved in the transfer of phosphate from ATP (also considered a co-factor in itself) to the substrate molecule. Other kinase co-factors include ionic species (such as zinc and calcium), lipids (such as phosphatidylinerine), and diacylglycerols.
In one embodiment of the method the one or more protein kinase(s) is a cyclin-dependent protein kinase. In a specific embodiment the cyclin-dependent kinase is a Group I CMCG kinase. In one embodiment the Group I CMCG kinase is selected from the group consisting of CDC2Hs, CDK2, CDK3, CDK4, CDK5, CDK6, CDK9, PCTAIRE1, PCTAIRE2, PCTAIRE3, CAK/MO15, Dm2, Dm2c, Ddc2, DdPRK, LmmCRKI, PIC2R, EhC2R, Cdc2R, cdc2+, CDC28, PHO85, KIN28, FpCdc2, MsCdc2B, and OsC2R or a functional equivalent thereof. In a specific embodiment the Group I CMCG kinase is CDK2 or a functional equivalent thereof.

In another embodiment of the method the one or more protein kinase(s) is a protein tyrosine kinase. In one form of this embodiment the protein tyrosine kinase is a Group VII protein tyrosine kinase. In one embodiment the Group VII protein tyrosine kinase is selected from the group consisting of TYK2, JAK1, JAK2 and HOP or a functional equivalent thereof. In a specific embodiment the Group VII protein tyrosine kinase is JAK2 or a functional equivalent thereof. In one form of the method, the JAK2 includes a recurrent unique acquired clonal mutation. This mutation is observed in a majority of polycytemia vera (PV) patients and a significant proportion of patients with other myeloproliferative disorders, including, essential thrombocytemia (ET) and chronic idiopathic myelofibrosis (IMF). In one form of the method the mutation is a valine to phenylalanine substitution at position 617 (V617F). The incidence of this mutation in PV patients is very high (around 78% of patients).

The JAK2 mutation is somatic and occurs at the level of a hematopoietic stem cell. Studies have demonstrated that the mutated JAK2 was found in myeloid cells, i.e., bone marrow cells, granulocytes, platelets and erythroblasts derived from CD34+ cells, but not in T cells. In addition, mutant JAK2 was found in hematopoietic colonies derived from hematopoietic progenitor cells. Applicant has demonstrated that kinase inhibitors described herein are capable of inhibiting the activity of wild type and mutant JAK2.

In another embodiment of the method the protein tyrosine kinase is a Group XIV protein tyrosine kinase. In one form of this embodiment the Group XIV protein tyrosine kinase is selected from the group consisting of PDGFR-b, PDGFR-a, CSF1R, c-kit, Flk2, FLT1, FLT2, FLT3 and FLT4 or a functional equivalent thereof. In one specific embodiment the Group XIV protein tyrosine kinase is FLT3 or a functional equivalent thereof. In another form of the method, the FLT3 kinase includes a mutation. There is
substantial experimental and clinical evidence to support the hypothesis that FLT3 mutations are important in the initiation or maintenance of AML in some patients. Activating mutations of FLT3 result in constitutive activation of FLT3 tyrosine kinase activity and can transform factor-dependent hematopoietic cells as evidenced by conversion to factor-independent growth and formation of tumours in immunodeficient mice. In addition, retroviral transduction of primary murine bone marrow with an AML patient-derived FLT3 ITD (internal tandem duplication) cDNA results in a lethal myeloproliferative syndrome. Furthermore, retroviral transduction of bone marrow derived from promyelocytic leukaemia/retinoic acid receptor (PML-RAR) transgenic mice with FLT3 ITD results in a marked increase in the incidence of acute progranulocytic (APL)-like leukaemia in such mice when compared with mice that received a transplant of mock-transduced bone marrow. Applicants have demonstrated that kinase inhibitors described herein are capable of inhibiting FLT3 including an ITD where there is a duplication of amino acids VDFREYEYDH at amino acid position 592-601. In an even more specific embodiment of the method the FLT3 includes an internal tandem duplication. In an even more specific embodiment the internal tandem duplication is a duplication of amino acids VDFREYEYDH at position 592-601.

In one embodiment of the method exposing the one or more protein kinase(s) to the compound includes administering the compound to a mammal containing the one or more protein kinase(s).

In one embodiment the one or more protein kinase(s) include at least two kinases selected from the group consisting of CDK2, FLT3 and JAK2 or functional equivalents thereof. In one form of this embodiment the one or more protein kinase(s) include all three of CDK2, FLT3 and JAK2 or functional equivalents thereof.

In an even further aspect the invention provides the use of a compound of the invention to inhibit one or more protein kinase(s).

In one embodiment the one or more protein kinase(s) is a cyclin-dependent protein kinase. In a specific embodiment the cyclin-dependent kinase is a Group I CMCG kinase. In one embodiment the Group I CMCG kinase is selected from the group consisting of CDC2Hs, CDK2, CDK3, CDK4, CDK5, CDK6, CDK9, PCTAIRE1, PCTAIRE2, PCTAIRE3, CAK/MO15, Dm2, Dm2c, Ddcdc2, DdPRK, LmmCRKI, PfC2R, EhC2R, CfCdc2R, cdc2+, CDC28, PHO85, KIN28, FpCdc2, MsCdc2B, and OsC2R and
functional equivalents thereof. In a specific embodiment the Group I CMCG kinase is CDK2 or a functional equivalent thereof.

In another embodiment the one or more protein kinase(s) is a protein tyrosine kinase. In one form of this embodiment the protein tyrosine kinase is a Group VII protein tyrosine kinase. In one embodiment the Group VII protein tyrosine kinase is selected from the group consisting of TYK2, JAK1, JAK2 and HOP or a functional equivalent thereof. In a specific embodiment the Group VII protein tyrosine kinase is JAK2 or a functional equivalent thereof. In a more specific embodiment the JAK2 includes a V to F mutation at position 617.

In another embodiment the protein tyrosine kinase is a Group XIV protein tyrosine kinase. In one form of this embodiment the Group XIV protein tyrosine kinase is selected from the group consisting of PDGFR-b, PDGFR-a, CSF1R, c-kit, Flk2, FLT1, FLT2, FLT3 and FLT4 or a functional equivalent thereof. In one specific embodiment the Group XIV protein tyrosine kinase is FLT3 or a functional equivalent thereof. In an even more specific embodiment FLT3 includes an internal tandem duplication. In an even more specific embodiment the internal tandem duplication is a duplication of amino acids VDFREYEDH at position 592-601.

In one embodiment the one or more protein kinase(s) include at least two kinases selected from the group consisting of CDK2, FLT3 and JAK2 or functional equivalents thereof. In one form of this embodiment the one or more protein kinase(s) include all three of CDK2, FLT3 and JAK2 or functional equivalents thereof.

In an even further aspect the invention provides a method of treating or preventing a condition in a mammal in which inhibition of one or more protein kinase(s) and/or co-factor(s) thereof prevents, inhibits or ameliorates a pathology or a symptomology of the condition, the method including administration of a therapeutically effective amount of a compound of the invention.

In one embodiment of the method the one or more protein kinase(s) is a cyclin-dependent protein kinase. In a specific embodiment the cyclin-dependent kinase is a Group I CMCG kinase. In one embodiment the Group I CMCG kinase is selected from the group consisting of CDC2Hs, CDK2, CDK3, CDK4, CDK5, CDK6, CDK9, PCTAIRE1, PCTAIRE2, PCTAIRE3, CAK/MO15, Dm2, Dm2c, Ddcdc2, DdPRK, LmmCRKI, PfC2R,
EhC2R, CfCdc2R, cdc2+, CDC28, PHO85, KIN28, FpCdc2, MsCdc2B, and OsC2R or a functional equivalent thereof. In a specific embodiment the Group I CMCG kinase is CDK2 or a functional equivalent thereof. In one embodiment the condition is selected from the group consisting of prostate cancer, retinoblastoma, malignant neoplasm of breast, malignant tumour of colon, endometrial hyperplasia, osteosarcoma, squamous cell carcinoma, non-small cell lung cancer, melanoma, liver cell carcinoma, malignant neoplasm of pancreas, myeloid leukaemia, cervical carcinoma, fibroid tumour, adenocarcinoma of the colon, T-cell leukaemia, glioma, glioblastoma, oligodendrogloma, lymphoma, ovarian cancer, restenosis, astrocytoma, bladder neoplasms, musculoskeletal neoplasms and Alzheimer's Disease.

In another embodiment of the method the one or more protein kinase(s) is a protein tyrosine kinase. In one form of this embodiment the protein tyrosine kinase is a Group VII protein tyrosine kinase. In one embodiment the Group VII protein tyrosine kinase is selected from the group consisting of TYK2, JAK1, JAK2 and HOP or a functional equivalent thereof. In a specific embodiment the Group VII protein tyrosine kinase is JAK2 or a functional equivalent thereof. In a more specific embodiment the JAK2 includes a V to F mutation at position 617. In one embodiment the condition is selected from the group consisting of Myeloproliferative disorders (chronic idiopathic myelofibrosis, polycythaemia vera, essential thrombocythaemia, chronic myeloid leukemia), myeloid metaplasia, chronic myelomonocytic leukaemia, acute lymphocytic leukaemia, acute erythoblastic leukaemia, Hodgkin’s disease, B-cell lymphoma, acute T-cell leukaemia, breast carcinoma, ovarian cancer, colon carcinoma, prostate cancer, melanoma, myelodysplastic syndromes, keloids, congestive heart failure, ischemia, thrombosis, cardiac hypertrophy, pulmonary hypertension, and retinal degeneration. In another embodiment the condition is an inflammatory disorder and/or an autoimmune disorder. Examples of disorders of this type that may be treated include acute disseminated encephalomyelitis, Addison’s disease, agammaglobulinemia, agranulocytosis, allergic asthma, allergic encephalomyelitis, allergic rhinitis, alopecia areata, alopecia senilis, anerythroplasia, ankylosing spondylitis, antiphospholipid antibody syndrome, aortitis syndrome, aplastic anemia, atopic dermatitis, autoimmune haemolytic anemia, autoimmune hepatitis, autoimmune oophoritis, Balo disease, Basedow’s disease, Behçet’s disease, bronchial asthma, Castleman’s syndrome, celiac disease, Chagas disease, chronic inflammatory demyelinating polyneuropathy, Churg-Strauss syndrome, Cogan’s syndrome, comical cornea, comical leukemia, Coxsackie myocarditis, CREST disease, Crohn’s disease, cutaneous eosinophilia, cutaneous T-cell lymphoma, dermatitis

In one specific embodiment the disorder is selected from the group consisting of ankylosing spondylitis, Graves' disease, inflammatory bowel diseases (Crohn's disease, ulcerative colitis), multiple sclerosis, psoriasis and rheumatoid arthritis.

In another embodiment of the method the protein tyrosine kinase is a Group XIV protein tyrosine kinase. In one form of this embodiment the Group XIV protein tyrosine kinase is selected from the group consisting of PDGFR-b, PDGFR-a, CSF1R, c-kit, Flk2, FLT1, FLT2, FLT3 and FLT4 or a functional equivalent thereof. In one specific embodiment the Group XIV protein tyrosine kinase is FLT3 or a functional equivalent thereof. In an even more specific embodiment FLT3 includes an internal tandem duplication. In an even more specific embodiment the internal tandem duplication is a duplication of amino acids VDFREYEDH at position 592-601. In one embodiment the condition is selected from the group consisting of acute myeloid leukemia, acute promyelocytic leukemia, acute lymphocytic leukemia, myelodysplastic syndromes, leukocytosis, juvenile myelomonocytic leukemia, acute B-cell leukemia, chronic myeloid
leukemia, acute T-cell leukemia, myeloproliferative disorders, and chronic myelomonocytic leukemia.

In one embodiment the one or more protein kinase(s) include at least two kinases selected from the group consisting of CDK2, FLT3 and JAK2 or functional equivalents thereof. In one form of this embodiment the one or more protein kinase(s) include all three of CDK2, FLT3 and JAK2 or functional equivalents thereof.

In an even further aspect the invention provides the use of a compound of the invention in the preparation of a medicament for treating a condition in an animal in which inhibition of one or more protein kinase(s) can prevent, inhibit or ameliorate the pathology or symptomology of the condition.

In one embodiment the one or more protein kinase(s) is a cyclin-dependent protein kinase. In a specific embodiment the cyclin-dependent kinase is a Group I CMCG kinase. In one embodiment the Group I CMCG kinase is selected from the group consisting of CDC2Hs, CDK2, CDK3, CDK4, CDK5, CDK6, CDK9, PCTAIRE1, PCTAIRE2, PCTAIRE3, CAK/MO15, Dm2, Dm2c, Ddcdc2, DdPRK, LmmCRKI, PIC2R, EhC2R, CfCdc2R, cdc2+, CDC28, PHO85, KIN28, FpCdc2, MsCdc2B, and OsC2R or a functional equivalent thereof. In a specific embodiment the Group I CMCG kinase is CDK2 or a functional equivalent thereof. In one embodiment the condition is selected from the group consisting of prostate cancer, retinoblastoma, malignant neoplasm of breast, malignant tumour of colon, endometrial hyperplasia, osteosarcoma, squamous cell carcinoma, non-small cell lung cancer, melanoma, liver cell carcinoma, malignant neoplasm of pancreas, myeloid leukemia, cervical carcinoma, fibroid tumour, adenocarcinoma of the colon, T-cell leukemia, glioma, glioblastoma, oligodendroglioma, lymphoma, ovarian cancer, restenosis, astrocytoma, bladder neoplasms, musculoskeletal neoplasms and Alzheimer's Disease.

In another embodiment the one or more protein kinase(s) is a protein tyrosine kinase. In one form of this embodiment the protein tyrosine kinase is a Group VII protein tyrosine kinase. In one embodiment the Group VII protein tyrosine kinase is selected from the group consisting of TYK2, JAK1, JAK2 and HOP or a functional equivalent thereof. In a specific embodiment the Group VII protein tyrosine kinase is JAK2 or a functional equivalent thereof. In a more specific embodiment the JAK2 includes a V to F mutation at position 617. In one embodiment the condition is selected from the group consisting of
Myeloproliferative disorders (chronic idiopathic myelofibrosis, polycythemia vera, essential thrombocythemia, chronic myeloid leukemia), myeloid metaplasia, chronic myelomonocytic leukemia, acute lymphocytic leukemia, acute erythroleukemia, Hodgkin's disease, B-cell lymphoma, acute T-cell leukemia, breast carcinoma, ovarian cancer, colon carcinoma, prostate cancer, melanoma, myelodysplastic syndromes, keloids, congestive heart failure, ischemia, thrombosis, cardiac hypertrophy, pulmonary hypertension, and retinal degeneration. In another embodiment the condition is an inflammatory disorder and/or an autoimmune disorder. Examples of disorders of this type that may be treated include acute disseminated encephalomyelitis, Addison's disease, agammaglobulinemia, agranulocytosis, allergic asthma, allergic encephalomyelitis, allergic rhinitis, alopecia areata, alopecia areata, anerythroplasia, ankylosing spondylitis, antiphospholipid antibody syndrome, aortitis syndrome, aplastic anemia, atop dermatitis, autoimmune haemolytic anemia, autoimmune hepatitis, autoimmune oophoritis, Balo disease, Basedow's disease, Behçet's disease, bronchial asthma, Castleman's syndrome, celiac disease, Chagas disease, chronic inflammatory demyelinating polyneuropathy, Churg-Strauss syndrome, Cogans syndrome, comical cornea, comical leukaemia, Coxsackie myocarditis, CREST disease, Crohn's disease, cutaneous eosinophilia, cutaneous T-cell lymphoma, dermatitis erythema multiforme, dermatomyositis, Dressler's syndrome, dystrophia epithelialis corneae, eczematous dermatitis, eosinophilic fasciitis, eosinophilic gastroenteritis, epidermolysis bullosa, Evans syndrome, fibrosing alveolitis, gestational pemphigoid, glomerulonephritis, Goodpasture's syndrome, graft-versus-host disease, Graves' disease, Guillain-Barre Syndrome, Hashimoto's disease, haemolytic-uretic syndrome, herpetic keratitis, ichthyosis vulgaris, idiopathic interstitial pneumonia, idiopathic thrombocytopenic purpura, inflammatory bowel diseases, Kawasaki's disease, keratitis, keratoconjunctivitis, Lambert-Eaton syndrome, leukoderma vulgaris, lichen planus, lichen sclerosus, Lyme disease, linear IgA disease, megaloblastic anemia, Meniere's disease, Mooren's ulcer, Mucha-Habermann disease, multiple myositis, multiple sclerosis, myasthenia gravis, necrotizing enterocolitis, neuromyelitis optica, ocular pemphigus, opsoclonus myoclonus syndrome, Ord's thyroiditis, paroxysmal nocturnal hemoglobinuria, Parsonnage-Turner syndrome, pemphigus, periodontitis, pernicious anemia, pollen allergies, polyglandular autoimmune syndrome, posterior uveitis, primary biliary cirrhosis, proctitis, pseudomembranous colitis, psoriasis, pulmonary emphysema, pyoderma, Reiter's syndrome, reversible obstructive airway disease, rheumatic fever, rheumatoid arthritis, sarcoidosis, scleritis, Sezary's syndrome, Sjögren's syndrome, subacute bacterial endocarditis, systemic lupus erythematosus, Takayasu's arteritis, temporal arteritis, Tolosa-Hunt syndrome, Type I
diabetes mellitus, ulcerative colitis, urticaria, vernal conjunctivitis, vitiligo, Vogt-Koyanagi-Harada syndrome and Wegener's granulomatosis.

In one specific embodiment the disorder is selected from the group consisting of ankylosing spondylitis, Graves' disease, inflammatory bowel diseases (Crohn's disease, ulcerative colitis), multiple sclerosis, psoriasis and rheumatoid arthritis.

In another embodiment the protein tyrosine kinase is a Group XIV protein tyrosine kinase. In one form of this embodiment the Group XIV protein tyrosine kinase is selected from the group consisting of PDGFR-b, PDGFR-a, CSF1R, c-kit, Flk2, FLT1, FLT2, FLT3 and FLT4 or a functional equivalent thereof. In one specific embodiment the Group XIV protein tyrosine kinase is FLT3 or a functional equivalent thereof. In an even more specific embodiment FLT3 includes an internal tandem duplication. In an even more specific embodiment the internal tandem duplication is a duplication of amino acids VDFREYEYDH at position 592-601. In one embodiment the condition is selected from the group consisting of acute myeloid leukemia, acute promyelocytic leukemia, acute lymphocytic leukemia, myelodysplastic syndromes, leukocytosis, juvenile myelomonocytic leukemia, acute B-cell leukemia, chronic myeloid leukemia, acute T-cell leukemia, myeloproliferative disorders, and chronic myelomonocytic leukemia.

In one embodiment the one or more protein kinase(s) include at least two kinases selected from the group consisting of CDK2, FLT3 and JAK2 or functional equivalents thereof. In one form of this embodiment the one or more protein kinase(s) include all three of CDK2, FLT3 and JAK2 or functional equivalents thereof.

In an even further aspect the invention provides the use of a compound of the invention in the preparation of a medicament for the treatment or prevention of a kinase-related disorder.

In one embodiment the kinase-related disorder is a proliferative disorder. In a specific embodiment the proliferative disorder is selected from the group consisting of myeloproliferative disorders (chronic idiopathic myelofibrosis, polycythaemia vera, essential thrombocytethemia, chronic myeloid leukaemia), myeloid metaplasia, chronic myelomonocytic leukaemia, acute myeloid leukaemia, juvenile myelomonocytic leukaemia, acute promyelocytic leukaemia, acute lymphocytic leukaemia, acute erythroblastic leukaemia, acute B-cell leukaemia, leukocytosis, Hodgkin's disease, B-cell lymphoma, acute T-cell leukaemia, breast carcinoma, ovarian cancer, colon carcinoma,
prostate cancer, melanoma, myelodysplastic syndromes, keloids, retinoblastoma, malignant neoplasm of breast, malignant tumour of colon, endometrial hyperplasia, osteosarcoma, squamous cell carcinoma, non-small cell lung cancer, melanoma, liver cell carcinoma, malignant neoplasm of pancreas, myeloid leukaemia, cervical carcinoma, fibroid tumour, adenocarcinoma of the colon, glioma, glioblastoma, oligodendroglioma, lymphoma, ovarian cancer, restenosis, astrocytoma, bladder neoplasms, and musculoskeletal neoplasms.

In one embodiment the proliferative disorder is a myeloproliferative disorder. In a specific embodiment the myeloproliferative disorder is selected from the group consisting of polycythemia vera, essential thrombocythemia and idiopathic myelofibrosis.

In another embodiment the proliferative disorder is cancer. In one embodiment the cancer is a solid tumour. In one embodiment the solid tumour is a tumour present in or metastasized from an organ or tissue selected from the group consisting of breast, ovary, colon, prostate, endometrium, bone, skin, lung, liver, pancreas, cervix, brain, neural tissue, lymphatic tissue, blood vessel, bladder and muscle.

In one embodiment the cancer is a haematological cancer. In a specific embodiment the haematological cancer is selected from the group consisting of acute myeloid leukaemia, acute promyelocyte leukaemia, acute lymphocytic leukaemia, myelodysplastic syndrome, leukocytosis, juvenile myelomonocytic leukaemia, acute B-cell leukaemia, chronic myeloid leukaemia, acute T-cell leukaemia, chronic myelomonocytic leukaemia, myeloid metaplasia, chronic myelomonocytic leukaemia, acute erythroblastic leukaemia, Hodgkin's disease, and B-cell lymphoma.

In another embodiment the condition is an inflammatory disorder and/or an autoimmune disorder. Examples of disorders of this type that may be treated include acute disseminated encephalomyelitis, Addison's disease, agammaglobulinemia, agranulocytosis, allergic asthma, allergic encephalomyelitis, allergic rhinitis, alopecia areata, alopecia senilis, anerythroplasia, ankylosing spondylitis, antiphospholipid antibody syndrome, aortitis syndrome, aplastic anemia, atopic dermatitis, autoimmune haemolytic anemia, autoimmune hepatitis, autoimmune oophoritis, Balo disease, Basedow's disease, Behcet's disease, bronchial asthma, Castleman's syndrome, celiac disease, Chagas disease, chronic inflammatory demyelinating polyneuropathy, Churg-Strauss syndrome, Cogans syndrome, comical cornea, comical leukoma, Coxsackie myocarditis, CREST

In one specific embodiment the disorder is selected from the group consisting of ankylosing spondylitis, Graves' disease, inflammatory bowel diseases (Crohn's disease, ulcerative colitis), multiple sclerosis, psoriasis and rheumatoid arthritis.

In another embodiment, the kinase-related disorder is a cardiovascular disorder. In one embodiment the cardiovascular disorder is selected from the group consisting of congestive heart failure, ischemia, thrombosis, cardiac hypertrophy and restenosis.

In one embodiment the kinase-related disorder is a neurodegenerative disorder. In a specific embodiment the neurodegenerative disorder is Alzheimer's disease.

In an even further aspect the invention provides a method of treating or preventing a kinase-related disorder including administration of a therapeutically effective amount of a compound of the invention to a patient in need thereof.
In one embodiment the kinase-related disorder is a proliferative disorder. In a specific embodiment the proliferative disorder is elected from the group consisting of myeloproliferative disorders (chronic idiopathic myelofibrosis, polycythemia vera, essential thrombocythemia, chronic myeloid leukaemia), myeloid metaplasia, chronic myelomonocytic leukaemia, acute myeloid leukaemia, juvenile myelomonocytic leukaemia, acute promyelocytic leukaemia, acute lymphocytic leukaemia, acute erythroblastic leukaemia, acute B-cell leukaemia, leukocytosis, Hodgkin's disease, B-cell lymphoma, acute T-cell leukaemia, breast carcinoma, ovarian cancer, colon carcinoma, prostate cancer, melanoma, myelodysplastic syndromes, keloids, retinoblastoma, malignant neoplasm of breast, malignant tumour of colon, endometrial hyperplasia, osteosarcoma, squamous cell carcinoma, non-small cell lung cancer, melanoma, liver cell carcinoma, malignant neoplasm of pancreas, myeloid leukaemia, cervical carcinoma, fibroid tumour, adenocarcinoma of the colon, glioma, glioblastoma, oligodendroglioma, lymphoma, ovarian cancer, restenosis, astrocytoma, bladder neoplasms, and musculoskeletal neoplasms.

In one embodiment the proliferative disorder is a myeloproliferative disorder. In a specific embodiment the myeloproliferative disorder is selected from the group consisting of polycythemia vera, essential thrombocythemia and idiopathic myelofibrosis.

In another embodiment the proliferative disorder is cancer. In one embodiment the cancer is a solid tumour. In one embodiment the solid tumour is a tumour present in or metastasized from an organ or tissue selected from the group consisting of breast, ovary, colon, prostate, endometrium, bone, skin, lung, liver, pancreas, cervix, brain, neural tissue, lymphatic tissue, blood vessel, bladder and muscle.

In one embodiment the cancer is a haematological cancer. In a specific embodiment the haematological cancer is selected from the group consisting of acute myeloid leukaemia, acute promyelocytic leukaemia, acute lymphocytic leukaemia, myelodysplastic syndrome, leukocytosis, juvenile myelomonocytic leukaemia, acute B-cell leukaemia, chronic myeloid leukaemia, acute T-cell leukaemia, chronic myelomonocytic leukaemia, myeloid metaplasia, chronic myelomonocytic leukaemia, acute erythroblastic leukaemia, Hodgkin's disease, and B-cell lymphoma.
In another embodiment the condition is an inflammatory disorder and/or an autoimmune disorder. Examples of disorders of this type that may be treated include acute disseminated encephalomyelitis, Addison's disease, agammaglobulinemia, agranulocytosis, allergic asthma, allergic encephalomyelitis, allergic rhinitis, alopecia areata, alopecia senilis, anerythroplasia, ankylosing spondylitis, antiphospholipid antibody syndrome, aortitis syndrome, aplastic anemia, atopic dermatitis, autoimmune haemolytic anemia, autoimmune hepatitis, autoimmune oophoritis, Balo disease, Basedow's disease, Behcet's disease, bronchial asthma, Castleman's syndrome, celiac disease, Chagas disease, chronic inflammatory demyelinating polyneuropathy, Churg-Strauss syndrome, Cogans syndrome, comical cornea, comical leukoma, Coxsackie myocarditis, CREST disease, Crohn's disease, cutaneous eosinophilia, cutaneous T-cell lymphoma, dermatitis hermaphroditism, dermatomyositis, Dressler's syndrome, dystrophia epidermolysis corneae, eczematous dermatitis, eosinophilic fasciitis, eosinophilic gastroenteritis, epidermolysis bullosa, Evans syndrome, fibrosing alveolitis, gestational pemphigoid, glomerulonephritis, Goodpasture's syndrome, graft-versus-host disease, Graves' disease, Guillain-Barre Syndrome, Hashimoto's disease, haemolytic-uremic syndrome, herpetiform keratitis, ichthyosis vulgaris, idiopathic interstitial pneumonia, idiopathic thrombocytopenic purpura, inflammatory bowel diseases, Kawasaki's disease, keratitis, keratoconjunctivitis, Lambert-Eaton syndrome, leukoderma vulgaris, lichen planus, lichen sclerosus, Lyme disease, linear IgA disease, megaloblastic anemia, Meniere's disease, Mooren's ulcer, Mucha-Habermann disease, multiple myositis, multiple sclerosis, myasthenia gravis, necrotizing enterocolitis, neuromyelitis optica, ocular pemphigus, opsoclonus myoclonus syndrome, Ord's thyroiditis, paroxysmal nocturnal hemoglobinuria, Parsonnage-Turner syndrome, pemphigus, periodontitis, pernicious anemia, pollen allergies, polyglandular autoimmune syndrome, posterior uveitis, primary biliary cirrhosis, proctitis, pseudomembranous colitis, psoriasis, pulmonary emphysema, pyoderma, Reiter's syndrome, reversible obstructive airway disease, rheumatic fever, rheumatoid arthritis, sarcoidosis, scleritis, Sezary's syndrome, Sjogren's syndrome, subacute bacterial endocarditis, systemic lupus erythematosus, Takayasu's arteritis, temporal arteritis, Tolosa-Hunt syndrome, Type I diabetes mellitus, ulcerative colitis, urticaria, vernal conjunctivitis, vitiligo, Vogt-Koyanagi-Harada syndrome and Wegener's granulomatosis.

In one specific embodiment the disorder is selected from the group consisting of ankylosing spondylitis, Graves' disease, inflammatory bowel diseases (Crohn's disease, ulcerative colitis), multiple sclerosis, psoriasis and rheumatoid arthritis.
In another embodiment, the kinase-related disorder is a cardiovascular disorder. In one embodiment the cardiovascular disorder is selected from the group consisting of congestive heart failure, ischemia, thrombosis, cardiac hypertrophy and restenosis.

In one embodiment the kinase-related disorder is a neurodegenerative disorder. In a specific embodiment the neurodegenerative disorder is Alzheimer's disease.

The invention also provides a method for inhibiting cell proliferation including administration of an effective amount of a compound according to formula (I).

DETAILED DESCRIPTION OF THE INVENTION

In this specification a number of terms are used which are well known to a skilled addressee. Nevertheless for the purposes of clarity a number of terms will be defined.

As used herein, the term "unsubstituted" means that there is no substituent or that the only substituents are hydrogen.

The term "optionally substituted" as used throughout the specification denotes that the group may or may not be further substituted or fused (so as to form a condensed polycyclic system), with one or more non-hydrogen substituent groups. In certain embodiments the substituent groups are one or more groups independently selected from the group consisting of halogen, =0, =S, -CN, -NO₂, -CF₃, -OCF₃, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkenyl, heterocycloalkylalkenyl, arylalkenyl, heteroarylalkenyl, cycloalkylheteroalkyl, heterocycloalkylheteroalkyl, arylheteroalkyl, heteroarylheteroalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyalkylalkyl, alkoxyheteroalkylalkyl, alkoxyaryl, alkoxyheteroaryl, alkoxy carbonyl, alkylaminocarbonyl, alkenyloxy, alkynyloxy, cycloalkyloxy, cycloalkynloxy, heterocycloalkyloxy, heterocycloalkynloxy, aryloxy, phenoxy, benzyloxy, heteroaryloxy, arylalkoxy, arylalkyl, heteroarylmethyl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkoxy, amino, alkyaminoo, acylaminoo, aminoalkyl, arylaminoo, sulfonilamino, sulfynilamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonil, sulfanyl, alkylsulfanyl, arylsulfanyl, aminosulfynilaminoalkyl, -COOH, -COR₆, -C(O)OR₆, CONHR₆, NHCOR₆, NHOOR₆, NHCONHR₆, C(=NOH)R₆, -SH, -SR₆, -OR₆ and acyl.
"Alkyl" as a group or part of a group refers to a straight or branched aliphatic hydrocarbon group, preferably a $C_1$-$C_{14}$ alkyl, more preferably $C_1$-$C_{10}$ alkyl, most preferably $C_1$-$C_6$ unless otherwise noted. Examples of suitable straight and branched $C_1$-$C_6$ alkyl substituents include methyl, ethyl, n-propyl, 2-propyl, n-butyl, sec-butyl, t-butyl, hexyl, and the like. The group may be a terminal group or a bridging group.

"Alkylamino" includes both mono-alkylamino and dialkylamino, unless specified. "Mono-alkylamino" means a -$NH$-$Alkyl$ group, in which alkyl is as defined above. "Dialkylamino" means a -$N(alkyl)_2$ group, in which each alkyl may be the same or different and are each as defined herein for alkyl. The alkyl group is preferably a $C_1$-$C_6$ alkyl group. The group may be a terminal group or a bridging group.

"Arylamino" includes both mono-arylamino and di-arylamino unless specified. Mono-arylamino means a group of formula aryl$NH$-, in which aryl is as defined herein. Di-arylamino means a group of formula (aryl)$_2$N- where each aryl may be the same or different and are each as defined herein for aryl. The group may be a terminal group or a bridging group.

"Acyl" means an alkyl-CO- group in which the alkyl group is as described herein. Examples of acyl include acetyl and benzoyl. The alkyl group is preferably a $C_1$-$C_6$ alkyl group. The group may be a terminal group or a bridging group.

"Alkenyl" as a group or part of a group denotes an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched preferably having 2-14 carbon atoms, more preferably 2-12 carbon atoms, most preferably 2-6 carbon atoms, in the normal chain. The group may contain a plurality of double bonds in the normal chain and the orientation about each is independently E or Z. Exemplary alkenyl groups include, but are not limited to, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl and nonenyl. The group may be a terminal group or a bridging group.

"Alkoxy" refers to an -O-alkyl group in which alkyl is defined herein. Preferably the alkoxy is a C1-C6 alkoxy. Examples include, but are not limited to, methoxy and ethoxy. The group may be a terminal group or a bridging group.
"Alkenyloxy" refers to an -O- alkenyl group in which alkenyl is as defined herein. Preferred alkenyloxy groups are C₁-C₆ alkenyloxy groups. The group may be a terminal group or a bridging group.

"Alkynyloxy" refers to an -O- alkynyl group in which alkynyl is as defined herein. Preferred alkynyloxy groups are C₁-C₆ alkynyloxy groups. The group may be a terminal group or a bridging group.

"Alkoxy carbonyl" refers to an -C(O)-O-alkyl group in which alkyl is as defined herein. The alkyl group is preferably a C₁-C₆ alkyl group. Examples include, but not limited to, methoxycarbonyl and ethoxycarbonyl. The group may be a terminal group or a bridging group.

"Alkylsulfinyl" means a -S(O)-alkyl group in which alkyl is as defined above. The alkyl group is preferably a C₁-C₆ alkyl group. Exemplary alkylsulfinyl groups include, but not limited to, methylsulfinyl and ethylsulfinyl. The group may be a terminal group or a bridging group.

"Alkylsulfonyl" refers to a -S(O)₂-alkyl group in which alkyl is as defined above. The alkyl group is preferably a C₁-C₆ alkyl group. Examples include, but not limited to, methylsulfonyl and ethylsulfonyl. The group may be a terminal group or a bridging group.

"Alkynyl" as a group or part of a group means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched preferably having from 2-14 carbon atoms, more preferably 2-12 carbon atoms, more preferably 2-6 carbon atoms in the normal chain. Exemplary structures include, but are not limited to, ethynyl and propynyl. The group may be a terminal group or a bridging group.

"Alkylaminocarbonyl" refers to an alkylamino-carbonyl group in which alkylamino is as defined above. The group may be a terminal group or a bridging group.

"Cycloalkyl" refers to a saturated or partially saturated, monocyclic or fused or spiro polycyclic, carbocycle preferably containing from 3 to 9 carbons per ring, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, unless otherwise specified. It includes monocyclic systems such as cyclopropyl and cyclohexyl, bicyclic systems such
as decalin, and polycyclic systems such as adamantane. The group may be a terminal group or a bridging group.

"Cycloalkenyl" means a non-aromatic monocyclic or multicyclic ring system containing at least one carbon-carbon double bond and preferably having from 5-10 carbon atoms per ring. Exemplary monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl or cycloheptenyl. The cycloalkenyl group may be substituted by one or more substituent groups. The group may be a terminal group or a bridging group.

The above discussion of alkyl and cycloalkyl substituents also applies to the alkyl portions of other substituents, such as without limitation, alkoxy, alkyl amines, alkyl ketones, arylalkyl, heteroarylalkyl, alkylsulfonyl and alkyl ester substituents and the like.

"Cycloalkylalkyl" means a cycloalkyl-alkyl group in which the cycloalkyl and alkyl moieties are as previously described. Exemplary monocycloalkylalkyl groups include cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl and cycloheptylmethyl. The group may be a terminal group or a bridging group.

"Halogen" represents chlorine, fluorine, bromine or iodine.

"Heterocycloalkyl" refers to a saturated or partially saturated monocyclic, bicyclic, or polycyclic ring containing at least one heteroatom selected from nitrogen, sulfur, oxygen, preferably from 1 to 3 heteroatoms in at least one ring. Each ring is preferably from 3 to 10 membered, more preferably from 4 to 7 membered. Examples of suitable heterocycloalkyl substituents include pyrrolidyl, tetrahydrofuryl, tetrahydrothiofuranyl, piperidyl, piperazyl, tetrahydropyranyl, morphilino, 1,3-diazapane, 1,4-diazapane, 1,4-oxazepane, and 1,4-oxathiapane. The group may be a terminal group or a bridging group.

"Heterocycloalkenyl" refers to a heterocycloalkyl as described above but containing at least one double bond. The group may be a terminal group or a bridging group.

"Heterocycloalkylalkyl" refers to a heterocycloalkyl-alkyl group in which the heterocycloalkyl and alkyl moieties are as previously described. Exemplary heterocycloalkylalkyl groups include (2-tetrahydrofuryl)methyl, (2-tetrahydrothiofuranyl)methyl. The group may be a terminal group or a bridging group.
"Heteroalkyl" refers to a straight- or branched-chain alkyl group preferably having from 2 to 14 carbons, more preferably 2 to 10 carbons in the chain, one or more of which has been replaced by a heteroatom selected from S, O, P and N. Exemplary heteroalkyls include alkyl ethers, secondary and tertiary alkyl amines, amides, alkyl sulfides, and the like. The group may be a terminal group or a bridging group. As used herein reference to the normal chain when used in the context of a bridging group refers to the direct chain of atoms linking the two terminal positions of the bridging group.

"Aryl" as a group or part of a group denotes (i) an optionally substituted monocyclic, or fused polycyclic, aromatic carbocycle (ring structure having ring atoms that are all carbon) preferably having from 5 to 12 atoms per ring. Examples of aryl groups include phenyl, naphthyl, and the like; (ii) an optionally substituted partially saturated bicyclic aromatic carbocyclic moiety in which a phenyl and a C₅₋₇ cycloalkyl or C₅₋₇ cycloalkenyl group are fused together to form a cyclic structure, such as tetrahydronaphthyl, indenyl or indanyl. The group may be a terminal group or a bridging group.

"Arylalkenyl" means an aryl-alkenyl- group in which the aryl and alkenyl are as previously described. Exemplary arylalkenyl groups include phenylallyl. The group may be a terminal group or a bridging group.

"Arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl moieties are as previously described. Preferred arylalkyl groups contain a C₅₋₇ alkyl moiety. Exemplary arylalkyl groups include benzyl, phenethyl and naphthelenemethyl. The group may be a terminal group or a bridging group.

"Heteroaryl" either alone or part of a group refers to groups containing an aromatic ring (preferably a 5 or 6 membered aromatic ring) having one or more heteroatoms as ring atoms in the aromatic ring with the remainder of the ring atoms being carbon atoms. Suitable heteroatoms include nitrogen, oxygen and sulphur. Examples of heteroaryl include thiophene, benzothiophene, benzo furan, benzimidazole, benzoazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furan, isoindolizine, xantholene, pheno xatine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indole, iso indole, 1H-indazole, purine, quinoline, isoquinoline, pthalazine, naphtthizine, quinoxaline, cinnoline, carbazole, phenanthridine, acridine, phenazine, thiazole, iso thiazole, phenothiazine, oxazole, isoaxazole, furazane, phenoxazine, 2-, 3- or A-pyridyl, 2-, 3-, 4-, 5-, or 8- quinolyl, 1-, 3-, A-, or 5- isoquinolinyl 1-, 2-, or 3- indolyl, and 2-, or 3-thienyl. The group may be a terminal group or a bridging group.
"Heteroarylalkyl" means a heteroaryl-alkyl group in which the heteroaryl and alkyl moieties are as previously described. Preferred heteroarylalkyl groups contain a lower alkyl moiety. Exemplary heteroarylalkyl groups include pyridylmethyl. The group may be a terminal group or a bridging group.

"Lower alkyl" as a group means unless otherwise specified, an aliphatic hydrocarbon group which may be straight or branched having 1 to 6 carbon atoms in the chain, more preferably 1 to 4 carbons such as methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary-butyl). The group may be a terminal group or a bridging group.

It is understood that included in the family of compounds of Formula (I) are isomeric forms including diastereoisomers, enantiomers, tautomers, and geometrical isomers in "E" or "Z" configurational isomer or a mixture of E and Z isomers. It is also understood that some isomeric forms such as diastereomers, enantiomers, and geometrical isomers can be separated by physical and/or chemical methods and by those skilled in the art.

Some of the compounds of the disclosed embodiments may exist as single stereoisomers, racemates, and/or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates and mixtures thereof, are intended to be within the scope of the subject matter described and claimed.

Additionally, Formula (I) is intended to cover, where applicable, solvated as well as unsolvated forms of the compounds. Thus, each formula includes compounds having the indicated structure, including the hydrated as well as the non-hydrated forms.

In addition to compounds of the Formula (I), the compounds of the various embodiments include pharmaceutically acceptable salts, prodrugs, N-oxides and active metabolites of such compounds, and pharmaceutically acceptable salts of such metabolites.

The term "pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the above-identified compounds, and include pharmaceutically acceptable acid addition salts and base addition salts. Suitable pharmaceutically acceptable acid addition salts of compounds of Formula (I) may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic
acids are hydrochloric, sulfuric, and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, heterocyclic carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, fumaric, maleic, alkyl sulfonic, arylsulfonic.

Suitable pharmaceutically acceptable base addition salts of compounds of Formula (I) include metallic salts made from lithium, sodium, potassium, magnesium, calcium, aluminium, and zinc, and organic salts made from organic bases such as choline, diethanolamine, morpholine. Other examples of organic salts are: ammonium salts, quaternary salts such as tetramethylammonium salt; amino acid addition salts such as salts with glycine and arginine. Additional information on pharmaceutically acceptable salts can be found in Remington's Pharmaceutical Sciences, 19th Edition, Mack Publishing Co., Easton, PA 1995. In the case of agents that are solids, it is understood by those skilled in the art that the inventive compounds, agents and salts may exist in different crystalline or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulae.

"Prodrug" means a compound which is convertible in vivo by metabolic means (e.g. by hydrolysis, reduction or oxidation) to a compound of formula (I). For example an ester prodrug of a compound of formula (I) containing a hydroxyl group may be convertible by hydrolysis in vivo to the parent molecule. Suitable esters of compounds of formula (I) containing a hydroxyl group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-β-hydroxynaphthoates, gestisates, isethionates, di-p-toluyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinates. As another example an ester prodrug of a compound of formula (I) containing a carboxy group may be convertible by hydrolysis in vivo to the parent molecule. (Examples of ester prodrugs are those described by F.J. Leinweber, Drug Metab. Res., 18:379, 1987).

The term "therapeutically effective amount" or "effective amount" is an amount sufficient to effect beneficial or desired clinical results. An effective amount can be administered in one or more administrations. An effective amount is typically sufficient to palliate, ameliorate, stabilize, reverse, slow or delay the progression of the disease state.

The term "normal chain" refers to the direct chain joining the two ends of a linking moiety. In reference to the present compounds an alkoxyalkyl group is a
heteroalkyl group containing a heteroatom in the normal chain (in this case an oxygen atom). An amide group is also a heteroalkyl group but it does not contain an oxygen atom in the normal chain (it has a nitrogen atom in the normal chain).

The term "functional equivalent" is intended to include variants of the specific protein kinase species described herein. It will be understood that kinases may have isoforms, such that while the primary, secondary, tertiary or quaternary structure of a given kinase isoform is different to the prototypical kinase, the molecule maintains biological activity as a protein kinase. Isoforms may arise from normal allelic variation within a population and include mutations such as amino acid substitution, deletion, addition, truncation, or duplication. Also included within the term "functional equivalent" are variants generated at the level of transcription. Many kinases (including JAK2 and CDK2) have isoforms that arise from transcript variation. It is also known that FLT3 has an isoform that is the result of exon-skipping. Other functional equivalents include kinases having altered post-translational modification such as glycosylation.

Specific compounds of the invention include the following:
The compounds of the invention have the ability to inhibit the activity of certain protein kinases. The ability to inhibit kinase activity may be a result of the compounds of the invention acting directly and solely on the kinase molecule to inhibit biological activity. However, it is understood that the compounds may also act at least partially on co-factors of the kinase in question that are involved in the phosphorylation process. For example, where the kinase is cyclin-dependent, a co-factor such as cyclinA is involved in the transfer of phosphate from ATP (also considered a co-factor in itself) to the substrate molecule. Other kinase co-factors include ionic species (such as zinc and calcium), lipids (such as phosphatidylserine), and diacylglycerols.

The compounds may have activity against a wide range of protein kinases. One suitable family of protein kinases are the cyclin-dependent protein kinases. An example of the cyclin-dependent kinases is the Group I CMCG kinases. Examples of Group I CMCG kinases include CDC2Hs, CDK2, CDK3, CDK4, CDK5, CDK6, CDK9, PCTAIRE1, PCTAIRE2, PCTAIRE3, CAK/MO15, Dm2, Dm2c, Ddc2c, DdPRK, LmmCRK1, PIC2R, EhC2R, CICdc2R, cdc2+, CDC28, PHO85, KIN28, FpCdc2, MsCdc2B, and OsC2R. A Group I CMCG kinase of particular interest is CDK2.

Another family of protein kinases are protein tyrosine kinases. An example of protein tyrosine kinases is a Group VII protein tyrosine kinase. Examples of Group VII protein tyrosine kinase include TYK2, JAK1, JAK2 and HOP. A protein kinase of particular interest is the Group VII protein tyrosine kinase JAK2. The JAK2 protein kinase may include a recurrent unique acquired clonal mutation. As stated previously this mutation is observed in a majority of polycythaemia vera (PV) patients and a significant proportion of patients with other myeloproliferative disorders, including, essential thrombocytomia (ET) and chronic idiopathic myelofibrosis (IMF). A typical mutation is a valine to phenylalanine substitution at position 617 (V617F). The incidence of this mutation in PV patients is very high (around 78% of patients).

Another example of protein tyrosine kinases is the Group XIV protein tyrosine kinases. Examples of the Group XIV protein tyrosine kinase include PDGFR-b, PDGFR-a, CSF1R, c-kit, Flik2, FLT1, FLT2, FLT3 and FLT4. A Group XIV protein tyrosine kinase of particular interest is FLT3. The FLT3 kinase may include a mutation. There is substantial experimental and clinical evidence to support the hypothesis that FLT3 mutations are important in the initiation or maintenance of AML in some patients. Activating mutations of FLT3 result in constitutive activation of FLT3 tyrosine kinase.
activity and can transform factor-dependent hematopoietic cells as evidenced by conversion to factor-independent growth and formation of tumours in immunodeficient mice. In addition, retroviral transduction of primary murine bone marrow with an AML patient-derived FLT3 ITD (internal tandem duplication) cDNA results in a lethal myeloproliferative syndrome. Furthermore, retroviral transduction of bone marrow derived from promyelocytic leukaemia/retinoic acid receptor (PML-RAR) transgenic mice with FLT3 ITD results in a marked increase in the incidence of acute progranulocytic (APL)-like leukaemia in such mice when compared with mice that received a transplant of mock-transduced bone marrow. Applicants have demonstrated that kinase inhibitors described herein are capable of inhibiting FLT3 including an ITD where there is a duplication of amino acids VDFREYEYDH at amino acid position 592-601. In an even more specific embodiment of the method the FLT3 includes an internal tandem duplication. In an even more specific embodiment the internal tandem duplication is a duplication of amino acids VDFREYEYDH at position 592-601.

The inhibition of the protein kinase may be carried out in any of a number of well known ways in the art. For example if inhibition of the protein kinase in vitro is desired an appropriate amount of the compound of the invention may be added to a solution containing the kinase. In circumstances where it is desired to inhibit the activity of the kinase in a mammal the inhibition of the kinase typically involves administering the compound to a mammal containing the kinase.

Accordingly the compounds of the invention may find a multiple number of applications in which their ability to inhibit protein kinases of the type mentioned above can be utilised. For example the compounds may be used to inhibit protein kinases. The compounds may also be used in treating or preventing a condition in a mammal in which inhibition of a protein kinase and/or co-factor thereof prevents, inhibits or ameliorates a pathology or a symptomology of the condition.

Examples of conditions that may be treated by inhibition of protein kinases include prostate cancer, retinoblastoma, malignant neoplasm of breast, malignant tumour of colon, endometrial hyperplasia, osteosarcoma, squamous cell carcinoma, non-small cell lung cancer, melanoma, liver cell carcinoma, malignant neoplasm of pancreas, myeloid leukemia, cervical carcinoma, fibroid tumour, adenocarcinoma of the colon, T-cell leukemia, glioma, glioblastoma, oligodendroglioma, lymphoma, ovarian cancer,
restenosis, astrocytoma, bladder neoplasms, musculoskeletal neoplasms and Alzheimer's Disease.

Other conditions that may be treated by inhibition of protein kinases include conditions such as Myeloproliferative disorders (chronic idiopathic myelofibrosis, polycytemia vera, essential thrombocytemia, chronic myeloid leukemia), myeloid metaplasia, chronic myelomonocytic leukemia, acute lymphocytic leukemia, acute erythroblastic leukemia, Hodgkin's disease, B-cell lymphoma, acute T-cell leukemia, breast carcinoma, ovarian cancer, colon carcinoma, prostate cancer, melanoma, myelodysplastic syndromes, keloids, congestive heart failure, ischemia, thrombosis, cardiac hypertrophy, pulmonary hypertension, and retinal degeneration.

Other conditions that may be treated by inhibition of protein kinases include acute myeloid leukemia, acute promyelocyte leukemia, acute lymphocytic leukemia, myelodysplastic syndromes, leukocytosis, juvenile myelomonocytic leukemia, acute B-cell leukemia, chronic myeloid leukemia, acute T-cell leukemia, myeloproliferative disorders, and chronic myelomonocytic leukemia.

The compounds of the invention may also be used the preparation of a medicament for treating a condition in an animal in which inhibition of a protein kinase can prevent, inhibit or ameliorate the pathology or symptomology of the condition. The compounds of the invention may also be used in the preparation of a medicament for the treatment or prevention of a kinase-related disorder.

One example of a kinase-related disorder is a proliferative disorder. In a specific embodiment the proliferative disorder is elected from the group consisting of myeloproliferative disorders (chronic idiopathic myelofibrosis, polycytemia vera, essential thrombocytemia, chronic myeloid leukaemia), myeloid metaplasia, chronic myelomonocytic leukaemia, acute myeloid leukaemia, juvenile myelomonocytic leukaemia, acute promyelocytic leukaemia, acute lymphocytic leukaemia, acute erythroblastic leukaemia, acute B-cell leukaemia, leukocytosis, Hodgkin's disease, B-cell lymphoma, acute T-cell leukaemia, breast carcinoma, ovarian cancer, colon carcinoma, prostate cancer, melanoma, myelodysplastic syndromes, keloids, retinoblastoma, malignant neoplasm of breast, malignant tumour of colon, endometrial hyperplasia, osteosarcoma, squamous cell carcinoma, non-small cell lung cancer, melanoma, liver cell carcinoma, malignant neoplasm of pancreas, myeloid leukaemia, cervical carcinoma,
fibroid tumour, adenocarcinoma of the colon, glioma, glioblastoma, oligodendroglioma, lymphoma, ovarian cancer, restenosis, astrocytoma, bladder neoplasms, and musculoskeletal neoplasms.

One example of a proliferative disorder is cancer. The cancer may be a solid tumour. The solid tumour may be a tumour present in or metastasized from an organ or tissue selected from the group consisting of breast, ovary, colon, prostate, endometrium, bone, skin, lung, liver, pancreas, cervix, brain, neural tissue, lymphatic tissue, blood vessel, bladder and muscle.

Another example of a cancer is a haematological cancer. Examples of haematological cancers include acute myeloid leukaemia, acute promyelocytic leukaemia, acute lymphocytic leukaemia, myelodysplastic syndrome, leukocytosis, juvenile myelomonocytic leukaemia, acute B-cell leukaemia, chronic myeloid leukaemia, acute T-cell leukaemia, chronic myelomonocytic leukaemia, myeloid metaplasia, chronic myelomonocytic leukaemia, acute erythroblastic leukaemia, Hodgkin's disease, and B-cell lymphoma.

Another kinase-related disorder is a cardiovascular disorder. Examples of cardiovascular disorder include congestive heart failure, ischemia, thrombosis, cardiac hypertrophy and restenosis.

Another kinase-related disorder is a neurodegenerative disorder. The neurodegenerative disorder may be Alzheimer's disease.

Another example of a kinase related disorder are inflammatory disorders and/or an autoimmune disorders. Examples of disorders of this type that may be treated include acute disseminated encephalomyelitis, Addison's disease, agammaglobulinemia, agranulocytosis, allergic asthma, allergic encephalomyelitis, allergic rhinitis, alopecia areata, alopecia senilis, anerythroplasia, ankylosing spondylitis, antiphospholipid antibody syndrome, aortitis syndrome, aplastic anemia, atopic dermatitis, autoimmune haemolytic anemia, autoimmune hepatitis, autoimmune oophoritis, Balo disease, Basedow's disease, Behcet's disease, bronchial asthma, Castleman's syndrome, celiac disease, Chagas disease, chronic inflammatory demyelinating polyneuropathy, Churg-Strauss syndrome, Cogans syndrome, comical cornea, comical leukemia, Coxsackie myocarditis, CREST disease, Crohn's disease, cutaneous eosinophilia, cutaneous T-cell lymphoma, dermatitis
erythema multiforme, dermatomyositis, Dressier\textsuperscript{a} syndrome, dystrophia epithelialis corneae, eczematous dermatitis, eosinophilic fasciitis, eosinophilic gastroenteritis, epidermolysis bullosa, Evans syndrome, fibrosing alveolitis, gestational pemphigoid, glomerulonephritis, Goodpasture\textquoteleft s syndrome, graft-versus-host disease, Graves\textquoteleft s disease, Guillain-Barre Syndrome, Hashimoto\textquoteleft s disease, haemolytic-uretic syndrome, herpetic keratitis, ichthyosis vulgaris, idiopathic interstitial pneumonia, idiopathic thrombocytopenic purpura, inflammatory bowel diseases, Kawasaki\textquoteleft s disease, keratitis, keratoconjunctivitis, Lambert-Eaton syndrome, leukoderma vulgaris, lichen planus, lichen sclerosus, Lyme disease, linear IgA disease, megaloblastic anemia, Meniere\textquoteleft s disease, Mooren\textquoteleft s ulcer, Mucha-Habermann disease, multiple myositis, multiple sclerosis, myasthenia gravis, necrotizing enterocolitis, neuromyelitis optica, ocular pemphigus, opsoconlonus myoclonus syndrome, Ord\textquoteleft s thyroiditis, paroxysmal nocturnal hemoglobinuria, Parsonnage-Turner syndrome, pemphigus, periodontitis, pelloncious anemia, pollen allergies, polyglandular autoimmune syndrome, posterior uveitis, primary biliary cirrhosis, proctitis, pseudomembranous colitis, psoriasis, pulmonary emphysema, pyoderma, Reiter\textquoteleft s syndrome, reversible obstructive airway disease, rheumatic fever, rheumatoid arthritis, sarcoidosis, scleritis, Sezary\textquoteleft s syndrome, Sjogren\textquoteleft s syndrome, subacute bacterial endocarditis, systemic lupus erythematosus, Takayasu\textquoteleft s arteritis, temporal arteritis, Tolosa-Hunt syndrome, Type I diabetes mellitus, ulcerative colitis, urticaria, vernal conjunctivitis, vitiligo, Vogy-Koyanagi-Harada syndrome and Wegener\textquoteleft s granulomatosis.

In one specific embodiment the inflammatory disorder is selected from the group consisting of ankylosing spondylitis, Graves\textquoteleft s disease, inflammatory bowel diseases (Crohn\textquoteleft s disease, ulcerative colitis), multiple sclerosis, psoriasis and rheumatoid arthritis...

The compounds disclosed have the ability to be used in the treatment of proliferative disorders. An example of such a disorder is cancer.

Administration of compounds within Formula (I) to humans can be by any of the accepted modes for enteral administration such as oral or rectal, or by parenteral administration such as subcutaneous, intramuscular, intravenous and intradermal routes. Injection can be bolus or via constant or intermittent infusion. The active compound is typically included in a pharmaceutically acceptable carrier or diluent and in an amount sufficient to deliver to the patient a therapeutically effective dose. In various embodiments the inhibitor compound may be selectively toxic or more toxic to rapidly proliferating cells, e.g. cancerous tumours, than to normal cells.
As used herein the term 'cancer' is a general term intended to encompass the vast number of conditions that are characterised by uncontrolled abnormal growth of cells.

It is anticipated that the compounds of the invention will be useful in treating various cancers including but not limited to bone cancers including Ewing's sarcoma, osteosarcoma, chondrosarcoma and the like, brain and CNS tumours including acoustic neuroma, neuroblastomas, glioma and other brain tumours, spinal cord tumours, breast cancers, colorectal cancers, advanced colorectal adenocarcinomas, endocrine cancers including adrenocortical carcinoma, pancreatic cancer, pituitary cancer, thyroid cancer, parathyroid cancer, thymus cancer, multiple endocrine neoplasia, gastrointestinal cancers including stomach cancer, oesophageal cancer, small intestine cancer, Liver cancer, extra hepatic bile duct cancer, gastrointestinal carcinoid tumour, gall bladder cancer, genitourinary cancers including testicular cancer, penile cancer, prostate cancer, gynaecological cancers including cervical cancer, ovarian cancer, vaginal cancer, uterus/endometrium cancer, vulva cancer, gestational trophoblastic cancer, fallopian tube cancer, uterine sarcoma, head and neck cancers including oral cavity cancer, lip cancer, salivary gland cancer, larynx cancer, hypopharynx cancer, orthopharynx cancer, nasal cancer, paranasal cancer, nasopharynx cancer, leukaemia's including childhood leukaemia, acute lymphocytic leukaemia, acute myeloid leukaemia, chronic lymphocytic leukaemia, chronic myeloid leukaemia, hairy cell leukaemia, acute promyelocytic leukaemia, plasma cell leukaemia, myelomas, haematological disorders including myelodysplastic syndromes, myeloproliferative disorders, aplastic anaemia, Fanconi anaemia, Waldenstrom's Macroglobulinemia, lung cancers including small cell lung cancer, non-small cell lung cancer, lymphomas including Hodgkin's disease, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, peripheral T-cell lymphoma, B-cell lymphoma, Burkitt's lymphoma, AIDS related Lymphoma, eye cancers including retinoblastoma, intraocular melanoma, skin cancers including melanoma, non-melanoma skin cancer, merkel cell cancer, soft tissue sarcomas such as childhood soft tissue sarcoma, adult soft tissue sarcoma, Kaposi's sarcoma, urinary system cancers including kidney cancer, Wilms tumour, bladder cancer, urethral cancer, and transitional cell cancer. Exemplary cancers that may be treated by compounds of this invention include Hematologic cancer such as myeloproliferative disorders (idiopathic myelofibrosis, polycythemia vera, essential thrombocythemia, chronic myeloid leukaemia), myeloid metaplasia, chronic myelomonocytic leukaemia, acute lymphocytic leukaemia, acute erythroleukemia, Hodgkin's and Non Hodgkin's disease, B-cell lymphoma, acute T-cell leukaemia, myelodysplastic syndromes, plasma cell disorder, hairy cell leukaemia,
kaposi's sarcoma, lymphoma; gynaecologic cancer such as breast carcinoma, ovarian cancer, cervical cancer, vaginal and vulva cancer, endometrial hyperplasia; gastrointestinal tract cancer such as colorectal carcinoma, polyps, liver cancer, gastric cancer, pancreatic cancer, gall bladder cancer; urinary tract cancer such as prostate cancer, kidney and renal cancer; urinary bladder cancer, urethral cancer, penile cancer; skin cancer such as melanoma; brain tumour such as glioblastoma, neuroblastoma, astrocytoma, ependynoma, brain-stem gliomas, medulloblastoma, menigiomas, astrocytoma, oligodendroglioma; head and neck cancer such as nasopharyngeal carcinoma, laryngeal carcinoma; respiratory tract cancer such as lung carcinoma (NSCLC and SCLC), mesothelioma; eye disease such as retinoblastoma; musculo-skeleton diseases such as osteosarcoma, musculoskeletal neoplasm; Squamous cell carcinoma and fibroid tumour.

Exemplary cancers that may be treated by compounds of this invention include but are not limited to bladder cancer, breast cancer, cervical cancer, colorectal cancer, colon cancer, gastric cancer, neuroblastoma, retinoblastoma, ovarian cancer, pancreatic cancer, leukaemia, lymphoma, prostate cancer and lung cancer.

Exemplary cancers that may be treated by compounds of this invention are colon cancer, colorectal cancer, pancreatic cancer and cervical cancer.

Even further exemplary cancers that may be treated by compounds of the present inventions include but are not limited to B-cell lymphoma (e.g. Burkitt's lymphoma), leukaemia (e.g. acute promyelocytic leukaemia, erythroleukemia), cutaneous T-cell lymphoma (CTCL) and peripheral T-cell lymphoma.

Even further exemplary cancers that may be treated by compounds of the present invention include solid tumours and hematologic malignancies.

It is anticipated that, by virtue of their JAK2 inhibition, the compounds of the invention will also be useful in treating various myeloproliferative disorders which may include polycythemia vera, essential thrombocythemia and idiopathic myelofibrosis.

In using the compounds of the invention they can be administered in any form or mode which makes the compound bioavailable. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending
upon the particular characteristics of the compound selected, the condition to be treated, the stage of the condition to be treated and other relevant circumstances. We refer the reader to Remingtons Pharmaceutical Sciences, 19th edition, Mack Publishing Co. (1995) for further information.

The compounds of the present invention can be administered alone or in the form of a pharmaceutical composition in combination with a pharmaceutically acceptable carrier, diluent or excipient. The compounds of the invention, while effective themselves, are typically formulated and administered in the form of their pharmaceutically acceptable salts as these forms are typically more stable, more easily crystallised and have increased solubility.

The compounds are, however, typically used in the form of pharmaceutical compositions which are formulated depending on the desired mode of administration. As such in a further embodiment the present invention provides a pharmaceutical composition including a compound of Formula (I) and a pharmaceutically acceptable carrier, diluent or excipient. The compositions are prepared in manners well known in the art.

The invention in other embodiments provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. In such a pack or kit can be found a container having a unit dosage of the agent(s). The kits can include a composition comprising an effective agent either as concentrates (including lyophilized compositions), which can be diluted further prior to use or they can be provided at the concentration of use, where the vials may include one or more dosages. Conveniently, in the kits, single dosages can be provided in sterile vials so that the physician can employ the vials directly, where the vials will have the desired amount and concentration of agent(s). Associated with such container(s) can be various written materials such as instructions for use, or a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

The compounds of the invention may be used or administered in combination with one or more additional drug(s) that are anti-cancer drugs and/or procedures (e.g. surgery, radiotherapy) for the treatment of the disorder/diseases mentioned. The
components can be administered in the same formulation or in separate formulations. If administered in separate formulations the compounds of the invention may be administered sequentially or simultaneously with the other drug(s).

In addition to being able to be administered in combination with one or more additional drugs that include anti-cancer drugs, the compounds of the invention may be used in a combination therapy. When this is done the compounds are typically administered in combination with each other. Thus one or more of the compounds of the invention may be administered either simultaneously (as a combined preparation) or sequentially in order to achieve a desired effect. This is especially desirable where the therapeutic profile of each compound is different such that the combined effect of the two drugs provides an improved therapeutic result.

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

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

If desired, and for more effective distribution, the compounds can be incorporated into slow release or targeted delivery systems such as polymer matrices, liposomes, and microspheres.
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The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

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

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

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

If desired, and for more effective distribution, the compounds can be incorporated into slow release or targeted delivery systems such as polymer matrices, liposomes, and microspheres.
The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

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

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

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

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

Dosage forms for topical administration of a compound of this invention include powders, patches, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers, or propellants which may be required.

The amount of compound administered will preferably treat and reduce or alleviate the condition. A therapeutically effective amount can be readily determined by an attending diagnostician by the use of conventional techniques and by observing results.
obtained under analogous circumstances. In determining the therapeutically effective amount a number of factors are to be considered including but not limited to, the species of animal, its size, age and general health, the specific condition involved, the severity of the condition, the response of the patient to treatment, the particular compound administered, the mode of administration, the bioavailability of the preparation administered, the dose regime selected, the use of other medications and other relevant circumstances.

A preferred dosage will be a range from about 0.01 to 300 mg per kilogram of body weight per day. A more preferred dosage will be in the range from 0.1 to 100 mg per kilogram of body weight per day, more preferably from 0.2 to 80 mg per kilogram of body weight per day, even more preferably 0.2 to 50 mg per kilogram of body weight per day. A suitable dose can be administered in multiple sub-doses per day.

As discussed above, the compounds of the embodiments may be useful for treating proliferative diseases. Examples of such cell proliferative diseases or conditions include cancer (include any metastases), psoriasis, and smooth muscle cell proliferative disorders such as restenosis. The inventive compounds may be particularly useful for treating tumours such as breast cancer, colon cancer, lung cancer, ovarian cancer, prostate cancer, head and/or neck cancer, or renal, gastric, pancreatic cancer and brain cancer as well as hematologic malignancies such as lymphoma and leukaemia. In addition, the inventive compounds may be useful for treating a proliferative disease that is refractory to the treatment with other anti-cancer drugs; and for treating hyperproliferative conditions such as leukemias, psoriasis and restenosis. In other embodiments, compounds of this invention can be used to treat pre-cancer conditions or hyperplasia including familial adenomatous polyposis, colonic adenomatous polyps, myeloid dysplasia, endometrial dysplasia, endometrial hyperplasia with atypia, cervical dysplasia, vaginal intraepithelial neoplasia, benign prostatic hyperplasia, papillomas of the larynx, actinic and solar keratosis, seborrheic keratosis and keratoacanthoma.

**SYNTHESIS OF COMPOUNDS OF THE INVENTION**

The agents of the various embodiments may be prepared using the reaction routes and synthesis schemes as described below, employing the techniques available in the art using starting materials that are readily available. The preparation of particular compounds of the embodiments is described in detail in the following examples, but the artisan will recognize that the chemical reactions described may be readily adapted to
prepare a number of other agents of the various embodiments. For example, the synthesis of non-exemplified compounds may be successfully performed by modifications apparent to those skilled in the art, e.g. by appropriately protecting interfering groups, by changing to other suitable reagents known in the art, or by making routine modifications of reaction conditions. A list of suitable protecting groups in organic synthesis can be found in T.W. Greene's Protective Groups in Organic Synthesis, 3rd, John Wiley & Sons, 1991. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the various embodiments.

Reagents useful for synthesizing compounds may be obtained or prepared according to techniques known in the art.

In the examples described below, unless otherwise indicated, all temperatures in the following description are in degrees Celsius and all parts and percentages are by weight, unless indicated otherwise.

Various starting materials and other reagents were purchased from commercial suppliers, such as Aldrich Chemical Company or Lancaster Synthesis Ltd., and used without further purification, unless otherwise indicated. Tetrahydrofuran (THF) and N,N-dimethylformamide (DMF) were purchased from Aldrich in SureSeal bottles and used as received. All solvents were purified by using standard methods in the art, unless otherwise indicated.

The reactions set forth below were performed under a positive pressure of nitrogen, argon or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents, and the reaction flasks are fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven-dried and/or heat-dried. Analytical thin-layer chromatography was performed on glass-backed silica gel 60 F 254 plates (E Merck (0.25 mm)) and eluted with the appropriate solvent ratios (v/v). The reactions were assayed by TLC and terminated as judged by the consumption of starting material.

The TLC plates were visualized by UV absorption or with a p-anisaldehyde spray reagent or a phosphomolybdic acid reagent (Aldrich Chemical, 20 wt% in ethanol) which was activated with heat, or by staining in an iodine chamber. Work-ups were typically done by doubling the reaction volume with the reaction solvent or extraction solvent and then washing with the indicated aqueous solutions using 25% by volume of the extraction
volume (unless otherwise indicated). Product solutions were dried over anhydrous sodium sulfate prior to filtration, and evaporation of the solvents was under reduced pressure on a rotary evaporator and noted as solvents removed in vacuo. Flash column chromatography [Still et al, J. Org. Chem., 43, 2923 (1978)] was conducted using E Merck-grade flash silica gel (47-61 mm) and a silica gel:crude material ratio of about 20:1 to 50:1, unless otherwise stated. Hydrogenolysis was done at the pressure indicated or at ambient pressure.

$^1$H NMR spectra were recorded on a Bruker instrument operating at 400 MHz, and $^{13}$C-NMR spectra was recorded operating at 100 MHz. NMR spectra are obtained as CDCl$_3$ solutions (reported in ppm), using chloroform as the reference standard (7.27 ppm and 77.00 ppm) or CD$_3$OD (3.4 and 4.8 ppm and 49.3 ppm), or an internal tetramethylsilane standard (0.00 ppm) when appropriate. Other NMR solvents were used as needed. When peak multiplicities are reported, the following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, br = broadened, dd = doublet of doublets, dt = doublet of triplets. Coupling constants, when given, are reported in Hertz.

Mass spectra were obtained using LC/MS either in ESI or APCI. All melting points are uncorrected.

All final products had greater than 90% purity (by HPLC at wavelengths of 220 nm and 254 nm).

The following examples are intended to illustrate the embodiments disclosed and are not to be construed as being limitations thereto. Additional compounds, other than those described below, may be prepared using the following described reaction scheme or appropriate variations or modifications thereof.
GENERAL SYNTHETIC SCHEME

Scheme 1 is a general synthetic scheme outlining the procedure for the preparation of compounds of general formula (VIII).

Scheme 1

\[
\begin{align*}
\text{(I)} & \quad \xrightarrow{\text{Suzuki}} \quad \text{(III)} \\
\text{(II)} & \quad \xrightarrow{\text{Suzuki}} \quad \text{(IV)} \\
\text{(V)} & \quad \xrightarrow{\text{Grubbs RCM}} \quad \text{(VIII)} \\
\text{(VI)} & \quad \xrightarrow{\text{Grubbs RCM}} \quad \text{(VII)}
\end{align*}
\]
In the examples described below, unless otherwise indicated, all temperatures in the following description are in degrees Celsius and all parts and percentages are by weight, unless indicated otherwise.

Example 1

Representative procedure for the synthesis of compounds type (VIII)

Preparation of Intermediates (III)

Example 1a

2-Chloro-4-(2-fluoro-pyridin-4-yl)-pyrimidine (IIIA)

To a degassed solution of 2,4-dichloropyrimidine (Ia) (0.85 g, 4.71 mmol) and 2-fluoropyridine-4-boronic acid (Ha) (1g, 7.14 mmol) in 1,2 dimethoxy ethane (20 mL) were added, sequentially, aqueous Na$_2$CO$_3$ (1.21 g, 11.42 mmol) and Pd(PPh$_3$)$_4$ (132 mg, 1.14 mmol). The resultant mixture was stirred at 80-85 °C for 4 h, cooled to 0°C and quenched with saturated NH$_4$Cl. The product was extracted with CH$_2$Cl$_2$ thrice and the combined organic extracts were washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude mixture was column purified (EtOAc/Hexane 1/5) to furnish 0.410 g of (IIIA) in 44% yield. LC-MS (ESI positive mode) m/z 210 ([M+H]$^+$); $^1$H NMR (400MHz, CDCl$_3$): δ 8.85 (d, 1H), 8.47 (d, 1H), 7.87 (dt, 1H), 7.75 (d, 1H), 7.67-7.68 (m, 1H).

Example 1b

2-Chloro-4-(2-fluoro-pyridin-4-yl)-5-methyl-pyrimidine (IIIB)
To a degassed solution of (lb) (1.5 g, 9.2 mmol) and (Ha) (1.62 g, 11.50 mmol) in 1,2 dimethoxy ethane (50 mL) were added, sequentially, aqueous Na$_2$CO$_3$ (1.90 g, 18.420 mmol) and Pd(PPh$_3$)$_4$ (0.53 g, 0.46 mmol). The resultant mixture was stirred at 80-85 °C for 4 h, cooled to O°C and quenched with saturated NH$_4$Cl. The product was extracted with CH$_2$Cl$_2$ thrice and the combined organic extracts were washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude mixture was column purified (EtOAc/Hexane 1/5) to furnish 0.500 g of (UIb) in 25 % yield. LC-MS (ESI positive mode) $m/z$ 224 ([IvHH]$^+$).

**Example 2**

**Preparation of Intermediates (IV)**

**Example 2a**

**Step 1.**

2-(2-Chloro-ethoxy)-5-nitro-benzaldehyde

![Reaction Scheme]

To a mixture of 2-hydroxy-5-nitrobenzaldehyde (1.Og, 5.98 mmol) and bromochloroethane (996 µl, 11.96 mmol) in dry DMF (15 mL) at ambient temperature was added potassium carbonate (1.64g, 11.96mmol) and the resulting mixture was stirred at 60°C overnight. The reaction mixture was cooled to O°C and quenched with H$_2$O. The product was extracted with CH$_2$Cl$_2$ thrice and the combined organic extracts were washed with H$_2$O followed by brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure to furnish 1.29g of 2-(2-chloro-ethoxy)-5-nitro-benzaldehyde as a yellow solid in 94% yield. LC-MS (ESI positive mode) $m/z$ 229 ([M+H]$^+$); $^1$H NMR (CDCl$_3$) δ 10.56 (s, 1H), 8.78 (d, 1H), 8.50 (dd, 1H), 7.15 (d, 1H), 4.54 (t, 2H), 3.99 (t, 2H).

**Step 2**

[2-(2-Chloro-ethoxy)-5-nitro-phenyl]-methanol

![Reaction Scheme]
To a solution of 2-(2-Chloro-ethoxy)-5-nitro-benzaldehyde (1g, 4.3 mmol) in MeOH (10mL) at ambient temperature was added NaBH₄ (160mg, 4.27mmol) and the resulting mixture was stirred for 30min. The reaction mixture was quenched with water. The product was extracted with CH₂Cl₂ thrice and the combined organic extracts were washed with H₂O followed by brine, dried over Na₂SO₄ and concentrated under reduced pressure to furnish without purification 1g of [2-(2-chloro-ethoxy)-5-nitro-phenyl]-methanol in 99% yield. LC-MS (ESI positive mode) m/z 232 ([M+H]+).

Step 3

2-Allyloxymethyl-1-(2-chloro-ethoxy)-4-nitro-benzene

To a mixture of [2-(2-chloro-ethoxy)-5-nitro-phenyl]-methanol (2 g, 8.63 mmol) and allyl bromide (2.99ml, 34.52 mmol) at ambient temperature was added KOH (2.98 ml, 34.52 mmol) and TBAI (159mg, 17.26 mmol) and the resulting mixture was stirred at 40°C overnight. The reaction mixture was cooled and quenched with H₂O. The product was extracted with CH₂Cl₂ thrice and the combined organic extracts were washed with H₂O followed by brine, dried over Na₂SO₄ and concentrated under reduced pressure to furnish an oil, which was purified by column (EtOAc/Hexane: 9/1) to obtain 2.1g of 2-allyloxymethyl-1-(2-chloro-ethoxy)-4-nitro-benzene in 89% yield. LC-MS (ESI positive mode) m/z 272 ([M+H]+).

Step 4

1-[2-<2-Allyloxymethyl-4-nitro-phenoxy)-ethyl]-pyrrolidine

To a solution of 2-allyloxymethyl-1-(2-chloro-ethoxy)-4-nitro-benzene (1g, 3.68 mmol) in DMA (10 mL) was added pyrrolidine (0.61mL, 7.36 mmol) and the resulting mixture was stirred overnight at 60°C. The reaction mixture was quenched with water. The
product was extracted with CH₂Cl₂ thrice and the combined organic extracts were washed with H₂O followed by brine, dried over Na₂SO₄ and concentrated under reduced pressure to furnish without purification 750 mg of 1-[2-(2-allyloxymethyl-4-nitro-phenoxy)-ethyl]-pyrrolidine with 70% yield. LC-MS (ESI positive mode) m/z 307 ([M+H]⁺).

Step 5
3-Allyloxymethyl-4-(2-pyrroldin-1-yl-ethoxy)-phenylamine (IVa)

To a solution of 1-[2-(2-allyloxymethyl-4-nitro-phenoxy)-ethyl]-pyrrolidine (750 mg, 0.23 mmol) in MeOH/CH₂Cl₂ (1:1, mL) at ambient temperature was added SnCl₂.2H₂O (207 mg, 0.92 mmol) and the resulting mixture was stirred overnight. The reaction mixture was cooled to 0°C and quenched with saturated Na₂CO₃. The product was extracted with CH₂Cl₂ thrice and the combined organic extracts were washed with H₂O followed by brine, dried over Na₂SO₄ and concentrated under reduced pressure to furnish an oil, which was purified by column (EtOAc/Hexane: 5/1) to obtain 486 mg of 3-allyloxymethyl-4-(2-pyrroldin-1-yl-ethoxy)-phenylamine (IVa) in 75% yield; LC-MS (ESI positive mode) m/z 277 ([M+H⁺]).

Example 2b
3-Allyloxymethyl-4-(3-pyrroldin-1-yl-propoxy)-phenylamine (IVb)

3-Allyloxymethyl-4-(3-pyrroldin-1-yl-propoxy)-phenylamine (IVb) was prepared in an analogous fashion to 3-allyloxymethyl-4-(2-pyrroldin-1-yl-ethoxy)-phenylamine (IVa) using the 4-step procedure described above with 1-bromo-3-chloropropane being used in place of bromochloroethane to alkylate the 2-hydroxy-5-nitrobenzaldehyde.

Example 2c
Preparation of 3-Allyloxymethyl-4-(4-methyl-piperazin-1-yl)-phenylamine (IVc)

Step 1

2-(4-Methyl-piperazin-1-yl)-5-nitro-benzaldehyde

To a stirred solution of 2-chloro-5-nitrobenzaldehyde (1g, 5.39 mmol) and K₂CO₃ (1.5g, 10.78 mmol) in DMF (20 ml.) was added 1-methylpiperazine (1.2ml, 10.78 mmol). The reaction mixture was heated to 90°C for 2 hours. Water was added, and the aqueous layer was extracted with EtOAc thrice. The combined organic layer was washed with water, brine, dried over Na₂SO₄, filtered and concentrated. 2-(4-Methyl-piperazin-1-yl)-5-nitro-benzaldehyde was purified via flash chromatography using an eluent gradient from 0-3% MeOH in CH₂Cl₂ and produced in 0.86g (64%).

Step 2

[2-(4-Methyl-piperazin-1-yl)-5-nitro-phenyl]-methanol

To a cooled, stirred solution of 2-(4-methyl-piperazin-1-yl)-5-nitro-benzaldehyde (0.86g, 3.45 mmol) in THF (8 mL) was added NaBH₄ (0.33, 8.66 mmol). MeOH (2 mL) was added slowly, and the reaction mixture was allowed to warm to room temp and stirred for a further 1 hour. It was then cooled to 0°C before 1M HCl was added until a clear solution formed. THF and MeOH were removed in vacuo, and the aqueous layer was
extracted with CH₂Cl₂ thrice. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude [2-(4-methyl-piperazin-1-yl)-5-nitrophenyl]-methanol was obtained in quantitative yield of 0.88 g.

**Step 3**

1-(2-Allyloxymethyl-4-nitro-phenyl)-4-methyl-piperazine

![Chemical structure](image)

To a mixture of [2-(4-methyl-piperazin-1-yl)-5-nitro-phenyl]-methanol (0.88 g, 3.51 mmol), potassium hydroxide (0.39 g, 7.0 mmol) and TBAHSO₄ (0.06 g, 0.17 mmol) was added allyl bromide (3 mL, excess). The reaction mixture was heated at 40°C for 1 hour. Upon cooling down to room temp water was added and allyl bromide was removed by *in vacuo*. The aqueous layer was extracted with CH₂Cl₂ thrice and the combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The 1-(2-allyloxymethyl-4-nitro-phenyl)-4-methyl-piperazine was purified via flash chromatography using mixed solvent of hexane and EtOAc (6:1) to obtain 0.46 g (46%).

**Step 4**

3-Allyloxymethyl-4-(4-methyl-piperazin-1-yl)-phenylamine (IVc)

![Chemical structure](image)

A mixture of 1-(2-allyloxymethyl-4-nitro-phenyl)-4-methyl-piperazine (0.46 g, 1.78 mmol) in EtOH (10 mL) was heated to around 50°C. Fe powder (0.3 g, 5.34 mmol) and NH₄Cl solution (saturated solution, 1 mL) were added. The reaction mixture was heated at reflux till completion of reduction. After cooling to room temp the mixture was filtered through celite and washed with ethyl acetate. Ethanol was removed *in vacuo* and water
added. The aqueous layer was extracted with CH₂Cl₂ thrice. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product (IVc) was obtained as dark yellow oil in 0.34g (73%).

Example 2d
Preparation of 2-Allyloxymethyl-N₁-(2-dimethylamino-ethyl)-N₁-methyl-benzene-1,4-diamine (IVd)

Step 1
2-[(2-Dimethylamino-ethyl)-methyl-amino]-5-nitro-benzaldehyde

\[ \text{To a stirred solution of 2-chloro-5-nitrobenzaldehyde (2g, 10.78 mmol) and K₂CO₃ (2.96g, 21.56 mmol) in DMF (40 mL) was added } \Lambda,\Lambda,\Lambda'-\text{trimethylethlenediamine (2.8mL, 21.56 mmol). The reaction mixture was heated to } 90^\circ\text{C for 2 hours. Water was added, and the aqueous layer was extracted with EtOAc thrice. The combined organic layers were washed with water, brine, dried over Na₂SO₄, filtered and concentrated. 2-[(2-Dimethylamino-ethyl)-methyl-amino]-5-nitro-benzaldehyde was purified via flash chromatography using gradient eluent from 0-3% MeOH in CH₂Cl₂ and produced in } 1.98g (73%). \]

Step 2
\{2-[(2-Dimethylamino-ethyl)-methyl-amino]-5-nitro-phenyl\}-methanol
To a cooled, stirred solution of 2-[[2-dimethylamino-ethyl]-methyl-amino]-5-nitro-benzaldehyde (1.98g, 7.88 mmol) in THF (35 mL) was added NaBH₄ (0.6g, 15.76 mmol). MeOH (5 mL) was added slowly and the reaction mixture was allowed to warm to room temp for another 1 hour. It was then cooled to 0°C before 1M HCl was added until a clear solution formed. THF and MeOH were removed in vacuo and the aqueous layer extracted with CH₂Cl₂ thrice. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude 2-[[2-dimethylamino-ethyl]-methyl-amino]-5-nitro-phenyl]-methanol was obtained in quantitative yield of 1.93g (97%).

**Step 3**
\[ \chi^{-}\text{-}(2\text{-allyloxymethyl-4-nitro-phenyl})/\chi^{-} \], \[ \chi^{-},\chi'^{-}\text{-trimethyl-ethane-1,2-diamine} \]

To a mixture of 2-[[2-dimethylamino-ethyl]-methyl-amino]-5-nitro-phenyl]-methanol (1.93g, 7.61 mmol), potassium hydroxide (0.61g, 15.22 mmol) and TBAHSO₄ (0.12g, 0.38 mmol) was added allyl bromide (3 mL, excess). The reaction mixture was heated at 40°C for 1 hour. Upon cooling down to room temp, water was added and allyl bromide was removed in vacuo. The aqueous layer was extracted with CH₂Cl₂ thrice and the combined organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated. \[ \chi^{-}\text{-}(2\text{-allyloxymethyl-4-nitro-phenyl})\text{-} \], \[ \chi^{-},\chi'^{-}\text{-trimethyl-ethane-1,2-diamine} \] was purified via flash chromatography using mixed solvent of hexane and EtOAc (6:1) to obtain 1.0g (45%).

**Step 4**
2-Allyloxymethyl- \[ \chi^{-}\text{-}(2\text{-dimethylamino-ethyl})\text{-} \] \[ \chi^{-}\text{-methyl-benzene-1,4-} \] diamine (IVd)
Λ'-{(2-Allyloxymethyl-4-nitro-phenyl)- Λ',Λ'-trimethyl-ethane-1,2-diamine (1.0g, 3.41 mmol) in EtOH (15 mL) heated to around 50°C. Fe powder (0.57g, 10.23 mmol) and NH₄Cl solution (saturated solution, 2ml) were added. The reaction mixture was heated at reflux until complete reduction was observed. Upon cooling down to room temp, the mixture was filtered through celite, washed with ethyl acetate. Ethanol was removed in vacuo, and water was added. The aqueous layer was extracted with CH₂Cl₂ thrice. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product (IVd) was obtained as dark yellow oil in 0.65g (72%).

Example 3
Preparation of Intermediates (V)

Example 3a
4-{2-[3-Allyloxymethyl-4-(2-pyrrolidin-1-yl-ethoxy)-phenylamino]-pyrimidin-4-yl}-pyridin-2-ol (Va)

To a mixture of (IIia) (280 mg, 1.33 mmol) and (IVa) (554 mg, 1.99 mmol) in MeOH (10 mL) at ambient temperature was added 1N HCl (1.0 mL) and the resulting mixture was stirred at 60°C overnight. The reaction mixture was cooled to 0°C and diluted with H₂O. The product was extracted with CH₂Cl₂ thrice and the combined organic extracts were washed with saturated NaHCO₃ followed by brine, dried over Na₂SO₄ and concentrated under reduced pressure to furnish an oil, which was purified by column (EtOAc/Hexane) to obtain 330 mg of (Va) in 55% yield. LC-MS (ESI positive mode) m/z
Example 3b

[3-Allyloxymethyl-4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-[4-(2-fluoro-pyridin-4-yl)-5-methyl-pyrimidin-2-yl]-amine (Vb)

To a mixture of (Ilb) (120 mg, 0.536 mmol) and (IVa) (222 mg, 0.805 mmol) in n-BuOH (10 mL) at ambient temperature was added 1N HCl (0.5 mL) and the resulting mixture was stirred at 90°C overnight. The reaction mixture was cooled to 0°C and concentrated under reduced pressure to furnish an oil, which was purified by Gilson to obtain 80 mg of (Vb) in 32% yield. LC-MS (ESI positive mode) m/z 464 ([M+H]+).

Example 3c

[3-Allyloxymethyl-4-(4-methyl-piperazin-1-yl)-phenyl]-[4-(2-fluoro-pyridin-4-yl)-pyrimidin-2-yl]-amine (Vc)

(Vc) was prepared in the same way as (Va) above.

Example 3d
2-Allyloxymethyl-N1-(2-dimethylamino-ethyl)-N4-[4-(2-fluoro-pyridin-4-yl)-pyrimidin-2-yl]-N1-methyl-benzene-1,4-diamine (Vd)

(Vd) was prepared in the same way as (Va) above.

Example 3e

[3-Allyloxymethyl-4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-[4-(2-fluoro-pyridin-4-yl)-pyrimidin-2-yl]-amine (Ve)

(Ve) was prepared in the same way as (Va) above.

Example 4

Preparation of Intermediates (VII)

Example 4a

[3-Allyloxymethyl-4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-[4-(2-but-3-enyloxy-pyridin-4-yl)-pyrimidin-2-yl]-amine (VIIa)
To a mixture of butanol (55 µl, 1.12 mmol) and sodium hydride (60% in oil) (55 mg, 1.4 mmol) in THF (10 mL) at 0 °C was added a solution of (Va) in THF (5 mL) and the resulting mixture was refluxed for 1.5 hours. The reaction mixture was cooled to 0 °C and quenched with H₂O. The product was extracted with CH₂Cl₂ thrice and the combined organic extracts were washed with saturated NaHCO₃ followed by brine, dried over Na₂SO₄ and concentrated under reduced pressure to furnish an oil, which was purified by preparative HPLC to obtain 220 mg of (V ila) in 78% yield. LC-MS (ESI positive mode) m/z 502 ([M+H]+).

**Example 4b**

[3-Allyloxymethyl-4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-[4-(2-but-3-enyloxy-pyridin-4-yl)-5-methyl-pyrimidin-2-yl]-amine (VIIb)

To a mixture of butanol (55 µl, 0.644 mmol) and sodium hydride (60% in oil) (55 mg, 1.4 mmol) in THF (10 mL) at 0 °C was added butanol (55 µl, 0.644 mmol) and stirred at 50 °C for 1 h and then a solution of (Vb) (75 mg, 0.161 mmol) in THF (5 mL) was added and the resulting mixture was refluxed overnight. The reaction mixture was cooled to 0 °C and quenched with H₂O and concentrated under reduced pressure to furnish an oil, which was purified by preparative HPLC to obtain 50 mg of (VIIb) in 60% yield. LC-MS (ESI positive mode) m/z 516 ([M+H]+).

**Example 4c**

[3-Allyloxymethyl-4-(4-methyl-piperazin-1-yl)-phenyl]-[4-(2-but-3-enyloxy-pyridin-4-yl)-pyrimidin-2-yl]-amine (VIIc)
(VIIc) was prepared in an analogous manner to (Vila).

Example 4d
2-Allyloxymethyl-N4-[4-(2-but-3-enyloxy-pyridin-4-yl)-pyrimidin-2-yl]-N1-(2-
dimethylamino-ethyl)-N1'-methyl-benzene-1,4-diamine (VIlld)

(VIIe) was prepared in an analogous manner to (Vila).

Example 4e
[3-Allyloxymethyl-4-(3-pyrrolidin-1-yl-propoxy)-phenyl]-[4-(2-but-3-enyloxy-
pyridin-4-yl]-pyrimidin-2-yl]-amine (VIIe)

(VIIe) was prepared in an analogous manner to (Vila).
Example 5
Preparation of Macrocycles (VIII)

Example 5a
Preparation of Compound 1

To a degassed solution of (Vila) (270 mg, 0.538 mmol) in CH₂Cl₂ (1 L) at ambient temperature was added Grubbs 2nd generation catalyst (68 mg, 0.08 mmol). The resulting mixture was stirred at 50°C for 4 hours. The reaction mixture was cooled and concentrated under reduced pressure to furnish an oil, which was purified by preparative HPLC to obtain 180 mg of compound 1 in 70% yield as a mixture of geometric isomers in a ratio of 67:33 (trans:cis). HPLC purity at 254 nm: 99%; LC-MS (ESI positive mode) m/z 474 ([IvHH]+).

Example 5b
Preparation of Compound 2

To a degassed solution of (Vilb) (50 mg, 0.069 mmol) in CH₂Cl₂ (100 mL) at ambient temperature was added Grubbs 2nd generation catalyst (8 mg, 0.009 mmol). The resulting mixture was stirred at 50°C for 4 hours. The reaction mixture was cooled and concentrated under reduced pressure to furnish an oil, which was purified by preparative
HPLC to obtain 20 mg of compound 2 in 43% yield as the predominant trans isomer.

HPLC purity at 254nm: 91%; LC-MS (ESI positive mode) m/z 487 ([M+H]+); 1H NMR (DMSO d6) δ 8.82 (d, 1H), 8.38 (s, 1H), 8.25 (d, 1H); 7.24-7.30 (m, 2H); 7.07-7.11 (m, 2H); 6.99-7.03 (m, 2H), 5.81-5.92 (m, 1H, J=15.4Hz); 5.54-5.64 (m, 1H, J=15.4Hz), 4.55-4.60 (m, 2H); 4.33-4.36 (m, 2H); 4.07 (d, 2H); 3.75-3.85 (m, 2H); 3.65-3.71 (m, 2H); 3.22-3.29 (m, 4H); 2.54-2.60 (m, 2H); 2.35 (s, 3H); 2.18-2.28 (m, 2H); 2.04-2.12 (m, 2H).

**Example 5c**

**Preparation of Compound 3**

Compound 3 was prepared using an identical procedure as for compound 1 above and isolated as the predominant trans isomer. LC-MS (ESI positive mode) m/z 459 ([M+HD]; 1H NMR (MeOD): δ 8.90 (d, 1H), 8.54 (d, 1H), 8.26 (d, 1H), 7.68 (d, 1H), 7.45 (dd, 1H), 7.31 (d, 1H), 7.17 - 7.13 (m, 1H), 7.10 - 7.07 (m, 1H), 5.88 - 5.59 (m, 2H), 4.62 (s, 2H), 4.60 (s, 2H), 4.54 (t, 2H), 4.11 (d, 2H), 3.62 - 3.57 (m, 2H), 3.46 - 3.35 (m, 4H), 3.14 - 3.09 (m, 2H), 3.00 (s, 3H).

**Example 5d**

**Preparation of Compound 4**

Compound 4 was prepared using an identical procedure as for compound 1 above and isolated as the predominant trans isomer. LC-MS (ESI positive mode) m/z 461
Example 5e
Preparation of Compounds 5 and 6

Compounds 5 and 6 were prepared using an identical procedure as for compound 1 above. The two geometric isomers were separated using preparative HPLC.

Compound 5 (cis): LC-MS (ESI positive mode) m/z 488 ([M+H]^+); ¹H NMR (MeOD) δ 8.41 (m, 1H), 8.27 (m, 1H), 8.10 (m, 1H), 7.71 (m, 1H), 7.38 (m, 1H), 7.24 (m, 1H), 6.99 (m, 1H), 6.90 (m, 1H), 5.65 (m, 2H), 4.54 (m, 2H), 4.31 (m, 2H), 4.21 (m, 2H), 4.09 (m, 2H), 3.65 (m, 2H), 3.38 (m, 2H), 3.03, (m, 2H), 2.46 (m, 2H), 2.17 (m, 2H), 2.08 (m, 2H), 1.95 (m, 2H).

Compound 6 (trans): LC-MS (ESI positive mode) m/z 488 ([M+H]^+); ¹H NMR (MeOD) δ 8.66 (m, 1H), 8.41 (m, 1H), 8.16 (m, 1H), 7.53 (m, 1H), 7.33 (m, 1H), 7.18 (m, 1H), 6.98 (m, 1H), 6.86 (m, 1H), 5.52-5.70 (m, 2H), 4.51 (m, 2H), 4.25 (m, 2H), 4.08 (m, 2H), 3.98 (m, 2H), 3.62 (m, 2H), 3.35 (m, 2H), 3.01 (m, 2H), 2.36 (m, 2H), 2.08 (m, 4H), 1.93 (m, 2H).
The data for the compounds synthesised above is outlined in Table 1.

<table>
<thead>
<tr>
<th>No</th>
<th>Structure</th>
<th>'HNMR (400 MHz)</th>
<th>m/z [MH]+</th>
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<td>1</td>
<td><img src="image1.png" alt="Structure Diagram" /></td>
<td>Isolated as a mixture of geometric isomers (67:33 trans:cis)</td>
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<tr>
<td>2</td>
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<td>(MeOD): δ 8.90 (d, 1H), 8.54 (d, 1H), 8.26 (d, 1H), 7.68 (d, 1H), 7.45 (dd, 1H), 7.31 (d, 1H), 7.17 – 7.13 (m, 1H), 7.10 – 7.07 (m, 1H), 5.88 – 5.59 (m, 2H), 4.62 (s, 2H), 4.60 (s, 2H), 4.54 (t, 2H), 4.11 (d, 2H), 3.62 – 3.57 (m, 2H), 3.46 – 3.35 (m, 4H), 3.14 – 3.09 (m, 2H), 3.00 (s, 3H)</td>
<td>459</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Structure Diagram" /></td>
<td>(MeOD): δ 9.04 (d, 1H), 8.58 (d, 1H), 8.29 (d, 1H), 7.72 (d, 1H), 7.47 (dd, 1H), 7.41 – 7.36 (m, 2H), 7.21 (dd, 1H), 5.99 – 5.66 (m, 2H), 4.63 (s, 2H), 4.60 (t, 2H), 4.26 (d, 2H), 3.39 (t, 2H), 3.10 (t, 2H), 2.89 (s, 6H), 2.76 (s, 3H)</td>
<td>461</td>
</tr>
<tr>
<td></td>
<td>3H), 2.53 – 2.47 (m, 2H)</td>
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<td></td>
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<tr>
<td>---</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(DMSO $d_6$) $\delta$ 8.82 (d, 1H), 8.38 (s, 1H), 8.25 (d, 1H); 7.24-7.30 (m, 2H); 7.07-7.11 (m, 2H); 6.99-7.03 (m, 2H), 5.81-5.92 (m, 1H, $J$=15.4Hz); 5.54-5.64 (m, 1H, $J$=15.4Hz), 4.55-4.60 (m, 2H); 4.33-4.36 (m, 2H); 4.07 (d, 2H); 3.75-3.85 (m, 2H); 3.65-3.71 (m, 2H); 3.22-3.29 (m, 4H); 2.54-2.60 (m, 2H); 2.35 (s, 3H); 2.18-2.28 (m, 2H); 2.04-2.12 (m, 2H).</td>
<td></td>
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</tr>
<tr>
<td>5</td>
<td>(MeOD) $\delta$ 8.41 (m, 1H), 8.27 (m, 1H), 8.10 (m, 1H), 7.71 (m, 1H), 7.38 (m, 1H), 7.24 (m, 1H), 6.99 (m, 1H), 6.90 (m, 1H), 5.65 (m, 2H), 4.54 (m, 2H), 4.31 (m, 2H), 4.21 (m, 2H), 4.09 (m, 2H), 3.65 (m, 2H), 3.38 (m, 2H), 3.03, (m, 2H), 2.46 (m, 2H), 2.17 (m, 2H), 2.08 (m, 2H), 1.95 (m, 2H)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(MeOD) $\delta$ 8.66 (m, 1H), 8.41 (m, 1H), 8.16 (m, 1H), 7.53 (m, 1H), 7.33 (m, 1H), 7.18 (m, 1H), 6.98 (m, 1H), 6.86 (m, 1H), 5.52-5.70 (m, 2H), 4.51 (m, 2H), 4.25 (m, 2H), 4.08 (m, 2H), 3.98 (m, 2H), 3.62 (m, 2H), 3.35 (m, 2H), 3.01 (m, 2H), 2.36 (m, 2H), 2.08 (m, 4H), 1.93 (m, 2H)</td>
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</table>
Following analogous procedures to the ones described above and by making appropriate modifications to the starting materials the compounds listed in Table 2 may also be made. Note: trans isomers only are shown. Cis isomers may also be prepared by the disclosed synthetic routes.

Table 2

<table>
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<tr>
<th>No</th>
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<td>52</td>
<td><img src="image2" alt="Chemical Structure 2" /></td>
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<td><img src="image4" alt="Chemical Structure 4" /></td>
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BIOLOGICAL TESTING

1. *In vitro* kinase activity assay

The recombinant enzymes (CDK2/CyclinA, FLT3, JAK2 and JAK2 V617F) were purchased from Invitrogen (Cat # PV3267, 3182, 4210 and 4347 respectively). All assays were carried out in 384-well white microtiter plates using the PKLight assay system from Cambrex (East Rutherford, New Jersey). This assay platform is essentially a luminometric assay for the detection of ATP in the reaction using a luciferase-coupled reaction. For CDK2/Cyclin A assay, the reaction mixture consisted of the following components in 25 µL assay buffer (50 mM Hepes pH 7.5, 10 mM MgCl₂, 5 mM MnCl₂, 5 mM BGP, 1 mM DTT, 0.1 mM sodium orthovanadate), 1.4 µg/mL of CDK2/Cyclin A complex, 0.5 µM of RbING substrate (Invitrogen, Cat # PV2939) and 0.5 µM of ATP. The compounds were tested at 8 concentrations prepared from 4-fold serial dilution starting at 10 µM. The reaction was incubated at room temperature for 2 hr. 13 µL of PKLight ATP detection reagent was added and the reaction was incubated for 10 min. Luminescence signals were detected on a multi-label plate reader (Victor² V 1420, Perkin-Elmer). The other kinase assays were identical except for the following differences in reagents. For FLT3 assays, the reaction contained 2.0 µg/mL FLT3 enzyme, 5 µM of poly(Glu.Tyr) substrate (Sigma, Cat # P0275) and 4 µM of ATP. For JAK2 assays, the reaction
contained 0.6 µg/mL of JAK2 enzyme, 2 µM of poly(Glu,Ala,Tyr) substrate (Sigma, Cat # P3899) and 0.2 µM of ATP. For JAK2 V617F mutant assays, the reaction contained 8.0 µg/mL of JAK2 mutant enzyme, 2 µM of poly(Glu,Ala,Tyr) substrate (Sigma, Cat # P3899) and 0.2 µM of ATP. The analytical software, Prism 4.0 (GraphPad Software Pte Ltd) was used to generate IC₅₀ values from the data. IC₅₀ is defined as the concentration of compound required for 50% inhibition of kinase enzyme activity.

**Comparative Examples**

In order to demonstrate the superiority of the compounds of the invention they were compared over a number of biological parameters to closely related compounds. The results of the comparisons are given in the following tables:

**Table 3 Comparative example 1 (Compound of Example 1)**

<table>
<thead>
<tr>
<th>Cmpd</th>
<th>JAK2 IC₅₀</th>
<th>CDK2 IC₅₀</th>
<th>CLogP</th>
<th>CLogD</th>
<th>TPSA</th>
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<tbody>
<tr>
<td><img src="image1.png" alt="Compound 1" /></td>
<td>0.052</td>
<td>7.6</td>
<td>4.06</td>
<td>4.17</td>
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<tr>
<td><img src="image2.png" alt="Compound 2" /></td>
<td>0.019</td>
<td>0.31</td>
<td>3.24</td>
<td>2.8</td>
<td>82</td>
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</table>

* All measurements of IC₅₀ are in micromolar

ClogP, clogD and TPSA were calculated in silico.

ClogP and TPSA were calculated using MOE V2006.08: which is available from Chemical Computing Group Suite 910 - 1010 Sherbrooke St. WMontreal, Quebec, Canada H3A 2R7.
ClogD was calculated using Pallas PrologD v2.01: which is available from CompuDrug International, Inc., 115 Morgan Drive, Sedona, AZ 86351, USA.

As can be seen the pyridyl compound shows marked improvement in comparison to the phenylene derivatives. The pyridyl compound shows improved JAK2 activity and is also a potent inhibitor of CDK2. In addition ClogP and ClogD of the pyridyl compounds are also improved indicating the improved drug like properties of this molecule.

Table 4 Comparative example 2 (Compound of Example 2)

<table>
<thead>
<tr>
<th>Cmpd</th>
<th>JAK2 IC50</th>
<th>CDK2 IC50</th>
<th>ClogP</th>
<th>ClogD</th>
<th>TPSA</th>
</tr>
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<tbody>
<tr>
<td><img src="image1.png" alt="Pyridyl Compound" /></td>
<td>0.041</td>
<td>9.0</td>
<td>3.2</td>
<td>4.1</td>
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<tr>
<td><img src="image2.png" alt="Phenylene Derivative" /></td>
<td>0.054</td>
<td>0.068</td>
<td>2.3</td>
<td>2.7</td>
<td>76</td>
</tr>
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</table>

* All measurements of IC50 are in micromolar

As can be seen the pyridyl compound shows marked improvement in comparison to the phenylene derivatives. Whilst having comparable JAK2 activity the pyridyl compound has remarkably improved CDK2 activity. In addition ClogP and ClogD of the pyridyl compound is also improved indicating the improved drug like properties of this molecule.

Table 5 Comparative example 3 (Compound of Example 6)
All measurements of IC₅₀ are in micromolar

As can be seen the pyridyl compound shows marked improvement in comparison to the phenylene derivatives. There is a remarkable difference between the CDK2 activity of the two compounds with the CDK2 activity of the pyridyl being an order of magnitude more potent. In addition CLogP and CLogD of the pyridyl compound is also improved indicating the improved drug like properties of this molecule.

In summary the pyridyl compounds of the invention show excellent CDK2 activity and in general have improved drug like properties when compared to the phenylene moieties.
Table 6 Kinase data for compounds 3 and 4

<table>
<thead>
<tr>
<th>Cmpd</th>
<th>Structure</th>
<th>JAK2 $\text{IC}_{50}$</th>
<th>CDK2 $\text{IC}_{50}$</th>
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<tr>
<td>3</td>
<td><img src="image" alt="Structure" /></td>
<td>0.26</td>
<td>0.54</td>
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<tr>
<td>4</td>
<td><img src="image" alt="Structure" /></td>
<td>0.015</td>
<td>3.4</td>
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</table>

The details of specific embodiments described in this invention are not to be construed as limitations. Various equivalents and modifications may be made without departing from the essence and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.
What is claimed is:

1. A compound of formula I:

![Chemical structure](image)

wherein:

- $R^1$ is selected from the group consisting of: H, halogen, OH, OCH₃, OCF₃, OCH₂CH₃, NO₂, NH₂, NHCH₃, NHCH₂CH₃, N(CH₃)₂, SH, SCH₃, optionally substituted C₁₋C₄ alkoxy, and optionally substituted CrC₄alkyl;

- each $R^2$ is independently selected from the group consisting of: H, halogen, OH, NO₂, CN, NH₂, optionally substituted d-C₃alkyl, optionally substituted C₂₋C₁₂ alkenyl, optionally substituted C₂₋C₁₂ alkylnyl, optionally substituted C₁₋C₃ heteroalkyl, optionally substituted C₃₋C₁₂ cycloalkyl, optionally substituted C₈₋C₉ aryl, optionally substituted d-d βheteroaryl, optionally substituted CrC₁₋C₀ alkoxy, optionally substituted C₂₋C₁₂ alkenyloxy, optionally substituted C₂₋C₁₂ alkynyloxy, optionally substituted d-C₁₀heteroa lkyloxy, optionally substituted C₃₋C₁₂ cycloalkenyloxy, optionally substituted C₁₋C₁₂ heterocycloalkenyloxy, optionally substituted C₆₋C₁₈ aryloxy, optionally substituted d-d βheteroaryloxy, optionally substituted d-C₃alkylamino, SR₄, SO₃H, SO₂NH₂, SO₂R₄, SONH₂, SOR₄, COR₄, COOH, COOR₄, CONHR₄, NHCOR₄, NHOOR₄, NHSO₂R₄, NHCONHR₄, NR₄R₅, and acyl;
each R₃ is independently selected from the group consisting of H, halogen, OH, NO₂, cyano, NH₂, optionally substituted CVC₃alkyl, optionally substituted C₂-C₁₂alkenyl, optionally substituted C₂-C₁₂alkynyl, optionally substituted C₃-C₁₂cycloalkyl, optionally substituted C₃-C₁₂cycloalkenyl, optionally substituted C₃-C₁₂heterocycloalkyl, optionally substituted C₃-C₁₂heterocycloalkenyl, optionally substituted C₆-C₁₈aryl, optionally substituted C₄-C₄heteroaryl, optionally substituted C₈-C₄heteroaryl; optionally substituted C₆-C₁₈aryloxy, optionally substituted C₇-C₇alkenyloxy, optionally substituted C₇-C₇alkynloxy, optionally substituted C₇-C₇alkynlyoxy, optionally substituted C₇-C₇heterocycloalkenyl, optionally substituted d-C₄heterocycloalkenyl, optionally substituted C₇-C₇heterocycloalkyloxy, optionally substituted C₆-C₁₈aryloxy, optionally substituted CrC₈heterocycloalkyloxy, optionally substituted d-C₄heterocycloalkyl, optionally substituted SR₄, SO₃H, SO₂NH₂, SO₂R₄, SONH₂, SOR₄, COR₄, COOH, COOR₄, CONHR₄, NHCOR₄, NHCOOR₄, NHCO₂R₄, NHCONHR₄, NR₄R₅, and acyl;

each R₄ and R₅ is independently selected from the group consisting of H, optionally substituted CrC₇alkyl, optionally substituted C₂-C₁₂alkenyl, optionally substituted C₂-C₁₂alkynyl, optionally substituted CrC₇heterocycloalkenyl, optionally substituted C₃-C₁₂cycloalkyl, optionally substituted C₃-C₁₂cycloalkenyl, optionally substituted CrC₇cycloalkenyl, optionally substituted CrC₇heterocycloalkenyl, optionally substituted C₆-C₁₈aryl, and optionally substituted CrC₈heteroaryl;

m is an integer selected from the group consisting of 0, 1, 2, and 3;

n is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

L is a group of formula:

\[-X¹-Y-X²⁻\]

wherein X¹ is attached to the pyridyl moiety and X² is attached to the phenyl moiety, and wherein X¹, X² and Y are selected such that the group L has between 5 and 15 atoms in the normal chain;

X¹ and X² are each independently a heteroalkyl group containing at least one oxygen atom in the normal chain,
Y is a group of formula \(-\text{CR}^a=\text{CR}^b\) or an optionally substituted cycloalkyl group,

wherein \(\text{R}^a\) and \(\text{R}^b\) are each independently selected from the group consisting of
H, and optionally substituted \(\text{C}_{1-12}\) alkyl;

or a pharmaceutically acceptable salt, N-oxide, or prodrug thereof.

2. A compound according to claim 1 wherein \(X^1\) is selected from the group

(a) \(-\text{OC}^\text{alkyl}\),
(b) \(-\text{C}_{1-5}\text{alkylO}\), and
(c) \(-\text{C}_{1-5}\text{alkylOC}_{1-5}\text{alkyl}\).

3. A compound according to claim 1 or 2 wherein \(X^1\) is selected from the group

(a) \(-\text{OCH}_2\),
(b) \(-\text{CH}_2\text{O}\),
(c) \(-\text{OCH}_2\text{CH}_2\),
(d) \(-\text{CH}_2\text{CH}_2\text{O}\),
(e) \(-\text{CH}_2\text{OCH}_2\), and
(f) \(-\text{CH}_2\text{CH}_2\text{OCH}_2\).

4. A compound according to any one of claims 1 to 3 wherein \(X^1\) is a group of the

formula:

\(-\text{OCH}_2\text{CH}_2\).

5. A compound according to any one of claims 1 to 4 wherein \(X^2\) is selected from
the group consisting of:

(a) \(-\text{OC}_{1-5}\text{alkyl}\),
(b) \(-\text{C}^\text{alkylO}\), and
(c) \(-\text{C}_{1-5}\text{alkylOC}_{1-5}\text{alkyl}\).

6. A compound according to any one of claims 1 to 5 wherein \(X^2\) is selected from
the group consisting of:

(a) \(-\text{OCH}_2\),
(b) \(-\text{CH}_2\text{O}\),
7. A compound according to any one of claims 1 to 6 wherein \( X^2 \) is a group of the formula:

\[-\text{CH}_2\text{OCH}_2^\cdot.\]

8. A compound according to claim 1 wherein the compound is of the formula:

\[
\begin{align*}
\text{R}_1 & \quad \text{N} \\
\text{N} & \quad \text{O} \\
\text{Y} & \quad \text{R}_2
\end{align*}
\]

wherein \( \text{R}_1, \text{R}_2, \text{R}_3, \text{Y}, m \) and \( n \) are as defined in claim 1.

9. A compound according to any one of claims 1 to 8 wherein \( \text{Y} \) is selected from the group consisting of:

\[
\begin{align}
\begin{array}{c}
\text{R}_1
\end{array}
\end{align}
\]

10. A compound according to any one of the preceding claims wherein \( \text{Y} \) is

\[
\begin{align}
\begin{array}{c}
\text{R}_1
\end{array}
\end{align}
\]

11. A compound according to any one of claims 1 to 9 wherein \( \text{Y} \) is
12. A compound according to claim 1 wherein the compound is of the formula:

wherein \( R, R, R, m, \) and \( n \) are as defined in claim 1.

13. A compound according to any one of the preceding claims wherein \( R^1 \) is selected from the group consisting of H, Cl, F, methyl, and methoxy.

14. A compound according to any one of the preceding claims wherein \( R^1 \) is H.

15. A compound according to any one of the preceding claims wherein \( R^2 \) is H.

16. A compound according to any one of the preceding claims wherein \( n \) is 0.

17. A compound according to any one of claims 1 to 15 wherein \( n \) is 1.

18. A compound according to any one of claims 1 to 15 or 17 wherein each \( R^3 \) is independently selected from the group consisting of optionally substituted \( d - C_{10} \) heteroalkyl, optionally substituted \( C_1-C_{10} \) heterocycloalkyl, and optionally substituted \( C_1-C_{12} \) alkoxy.
19. A compound according to claim 18 wherein $R^3$ is an optionally substituted $C_1$-$C_{12}$ alkyloxy of the formula:

\[
\begin{array}{c}
\text{A} \\
\text{B} \\
\text{D} \\
\text{R}^{10}
\end{array}
\]

wherein

- $A$ is selected from the group consisting of a bond, $O$, and $CH_2$;
- $B$ is selected from the group consisting of $O$ and $CH_2$;

with the proviso that only one of $A$ and $B$ is $O$;

- $D$ is selected from the group consisting of $N$ and $CR^{12}$;
- $p$ is an integer selected from the group consisting of $0$, $1$, $2$, $3$, $4$, $5$, and $6$;

$R^{10}$ and $R^{11}$ are independently selected from the group consisting of $H$, optionally substituted $Ci-Ci_2$ alkyl, optionally substituted $C_2-C_{12}$ alkenyl, optionally substituted $C_2-C_{12}$ alkynyl, optionally substituted $C_1-C_{12}$ heteroalkyl, optionally substituted $C_3-C_{12}$ cycloalkyl, optionally substituted $C_3-C_{12}$ cycloalkenyl, optionally substituted $C_1-C_{12}$ heterocycloalkyl, optionally substituted $C_6-C_{18}$aryl, and optionally substituted $Ci-C_{18}$ heteroaryl, or

$R^{10}$ and $R^{11}$ when taken together with the atom to which they are attached form an optionally substituted cyclic moiety;

$R^{12}$ is $H$ or optionally substituted $C_1-C_6$ alkyl.

20. A compound according to any one of claim 1 to 15 and 17-18 wherein each $R^3$ is independently selected from the group consisting of:
21. A compound according to any one of claims 1 to 20 wherein each optional substituent is independently selected from the group consisting of: halogen, =0, =S, CN, NO₂, CF₃, OCF₃, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, hydroxy, hydroxalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkoxyheteroaryl, alkenyloxy, alkynyloxy, cycloalkyloxy, cycloalkenylxy, heterocycloalkyloxy, heterocycloalkenylxy, aryloxy, heteroaryloxy, arylalkyl, heteroaryalkyl, arylalkyloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, aminoalkyl, alkoxyalkyl, COOH, COR⁶, C(O)OR⁶, SH₁, SR⁶, OR⁶ and acyl, each of which may be optionally substituted, and

R⁶ is H, optionally substituted Ci-Ci₂ alkyl, optionally substituted C₂-Ci₄ alkenyl, optionally substituted C₂-Ci₂ alkynyl, optionally substituted CrC⁶ heteroalkyl, optionally substituted C₃-Ci₂ cycloalkyl, substituted C₃-Ci₂ cycloalkenyl, optionally substituted C₁-Ci₂ heterocycloalkyl, optionally substituted Ci-Ci₈ heteroaryalkyl, and acyl.

22. A compound according to claim 1 selected from the group consisting of:
or a pharmaceutically acceptable salt or prodrug thereof.

23. A pharmaceutical composition including a compound according to any one of claims 1 to 22 and a pharmaceutically acceptable diluent, excipient or carrier.

24. A method of inhibiting one or more protein kinase(s) including exposing the one or more protein kinase(s) and/or co-factor(s) thereof to an effective amount of a compound according to any one of claims 1 to 23.

25. A method according to claim 24 wherein the one or more protein kinase(s) is a cyclin-dependent protein kinase.

26. A method according to claim 25 wherein the cyclin-dependent kinase is a Group I CMCG kinase.

27. A method according to claim 26 wherein the Group I CMCG kinase is selected from the group consisting of CDC2Hs, CDK2, CDK3, CDK4, CDK5, CDK6, CDK9, PCTAIRE1, PCTAIRE2, PCTAIRE3, CAK/MO15, Dm2, Dm2c, Ddc2c2, DdPRK, LmmCRKI, PIC2R, EhC2R, Cdc2R, cdc2+, CDC28, PHO85, KIN28, FpCdc2, MsCdc2B, and OsC2R or a functional equivalent thereof.
28. A method according to claim 26 or 27 wherein the Group I CMCG kinase is CDK2 or a functional equivalent thereof.

29. A method according to claim 24 wherein the one or more protein kinase(s) is a protein tyrosine kinase.

30. A method according to claim 29 wherein the protein tyrosine kinase is a Group VII protein tyrosine kinase.

31. A method according to claim 30 wherein the Group VII protein tyrosine kinase is selected from the group consisting of TYK2, JAK1, JAK2 and HOP or a functional equivalent thereof.

32. A method according to claim 30 or 31 wherein the Group VII protein tyrosine kinase is JAK2 or a functional equivalent thereof.

33. A method according to claim 32 wherein the JAK2 includes a V to F mutation at position 617.

34. A method according to claim 29 wherein the protein tyrosine kinase is a Group XIV protein tyrosine kinase.

35. A method according to claim 34 wherein the Group XIV protein tyrosine kinase is selected from the group consisting of PDGFR-b, PDGFR-a, CSF1R, c-kit, Flk2, FLT1, FLT2, FLT3 and FLT4 or a functional equivalent thereof.

36. A method according to claim 34 or 35 wherein the Group XIV protein tyrosine kinase is FLT3 or a functional equivalent thereof.

37. A method according to claim 36 wherein the FLT3 includes an internal tandem duplication.

38. A method according to claim 37 wherein the internal tandem duplication is a duplication of amino acids VDFREYEYDH at position 592-601.
39. A method according to any one of claims 24 to 38 wherein exposing the one or more protein kinase(s) to the compound includes administering the compound to a mammal containing the one or more protein kinase(s).

40. A method according to claim 24 wherein the one or more protein kinase(s) include at least two kinases selected from the group consisting of CDK2, FLT3 and JAK2 or functional equivalents thereof.

41. A method according to claim 40 wherein the one or more protein kinase(s) include all three of CDK2, FLT3 and JAK2 or functional equivalents thereof.

42. Use of a compound according to any one of claims 1 to 22 to inhibit one or more protein kinase(s).

43. A use according to claim 42 wherein the one or more protein kinase(s) is a cyclin-dependent protein kinase.

44. A use according to claim 43 wherein the cyclin-dependent kinase is a Group I CMCG kinase.

45. A use according to claim 44 wherein the Group I CMCG kinase is selected from the group consisting of, CDC2Hs, CDK2, CDK3, CDK4, CDK5, CDK6, CDK9, PCTAIRE1, PCTAIRE2, PCTAIRE3, CAK/MO15, Dm2, Dm2c, Ddcdc2, DdPRK, LmmCRKI, PIC2R, EhC2R, CfCdc2R, cdc2+, CDC28, PHO85, KIN28, FpCdc2, MsCdc2B, and OsC2R or a functional equivalent thereof.

46. A use according to claim 44 or 45 wherein the Group I CMCG kinase is CDK2.

47. A use according to claim 42 wherein the one or more protein kinase(s) is a protein tyrosine kinase.

48. A use according to claim 47 wherein the protein tyrosine kinase is a Group VII protein tyrosine kinase.
49. A use according to claim 48 wherein the Group VII protein tyrosine kinase is selected from the group consisting of TYK2, JAK1, JAK2 and HOP or a functional equivalent thereof.

50. A use according to claim 48 or 49 wherein the Group VII protein tyrosine kinase is JAK2 or a functional derivative thereof.

51. A use according to claim 50 wherein the JAK2 includes a V to F mutation at position 617.

52. A use according to claim 47 wherein the protein tyrosine kinase is a Group XIV protein tyrosine kinase.

53. A use according to claim 52 wherein the Group XIV protein tyrosine kinase is selected from the group consisting of PDGFR-b, PDGFR-a, CSF1R, c-kit, Flk2, FLT1, FLT2, FLT3 and FLT4 or a functional equivalent thereof.

54. A use according to claim 53 wherein the Group XIV protein tyrosine kinase is FLT3 or a functional equivalent thereof.

55. A use according to claim 54 wherein the FLT3 includes an internal tandem duplication.

56. A use according to claim 55 wherein the internal tandem duplication is a duplication of amino acids VDFREYEDH at position 592-601.

57. A use according to claim 42 wherein the one or more protein kinase(s) include at least two kinases selected from the group consisting of CDK2, FLT3 and JAK2 or functional equivalents thereof.

58. A use according to claim 57 wherein the one or more protein kinase(s) include all three of CDK2, FLT3 and JAK2 or functional equivalents thereof.

59. A method of treating or preventing a condition in a mammal in which inhibition of one or more protein kinase(s) and/or co-factor(s) thereof prevents, inhibits or ameliorates
a pathology or a symptomology of the condition, the method including administration of a therapeutically effective amount of a compound according to any one of claims 1 to 22.

60. A method according to claim 59 wherein the one or more protein kinase(s) is a cyclin-dependent protein kinase.

61. A method according to claim 60 wherein the cyclin-dependent kinase is a Group I CMCG kinase.

62. A method according to claim 61 wherein the Group I CMCG kinase is selected from the group consisting of CDC2Hs, CDK2, CDK3, CDK4, CDK5, CDK6, CDK9, PCTAIRE1, PCTAIRE2, PCTAIRE3, CAK/M015, Dm2, Dm2c, Ddcdc2, DdPRK, LmmCRKI, PIC2R, EhC2R, CFCdc2R, cdc2+, CDC28, PHO85, KIN28, FpCdc2, MsCdc2B, and OsC2R or a functional equivalent thereof.

63. A method according to claim 61 or 62 wherein the Group I CMCG kinase is CDK2 or a functional equivalent thereof.

64. A method according to any one of claims 60 to 63 wherein the condition is selected from the group consisting of prostate cancer, retinoblastoma, malignant neoplasm of breast, malignant tumour of colon, endometrial hyperplasia, osteosarcoma, squamous cell carcinoma, non-small cell lung cancer, melanoma, liver cell carcinoma, malignant neoplasm of pancreas, myeloid leukemia, cervical carcinoma, fibroid tumour, adenocarcinoma of the colon, T-cell leukemia, glioma, glioblastoma, oligodendroglioma, lymphoma, ovarian cancer, restenosis, astrocytoma, bladder neoplasms, musculoskeletal neoplasms and Alzheimer’s Disease.

65. A method according to claim 59 wherein the one or more protein kinase(s) is a protein tyrosine kinase.

66. A method according to claim 65 wherein the protein tyrosine kinase is a Group VII protein tyrosine kinase.

67. A method according to claim 66 wherein the Group VII protein tyrosine kinase is selected from the group consisting of TYK2, JAK1, JAK2 and HOP or a functional equivalent thereof.
68. A method according to claim 67 wherein the Group VII protein tyrosine kinase is JAK2 or a functional equivalent thereof.

69. A method according to claim 68 wherein the JAK2 includes a V to F mutation at position 617.

70. A method according to any one of claims 65 to 69 wherein the condition is selected from the group consisting of Myeloproliferative disorders (chronic idiopathic myelofibrosis, polycythemia vera, essential thrombocythemia, chronic myeloid leukemia), myeloid metaplasia, chronic myelomonocytic leukemia, acute lymphocytic leukemia, acute erythroid leukemia, Hodgkin's disease, B-cell lymphoma, acute T-cell leukemia, breast carcinoma, ovarian cancer, colon carcinoma, prostate cancer, melanoma, myelodysplastic syndromes, keloids, congestive heart failure, ischemia, thrombosis, cardiac hypertrophy, pulmonary hypertension, and retinal degeneration.

71. A method according to any one of claims 66 to 69 wherein the condition is an inflammatory disorder or an autoimmune disorder selected from the group consisting of acute disseminated encephalomyelitis, Addison's disease, agammaglobulinemia, agranulocytosis, allergic asthma, allergic encephalomyelitis, allergic rhinitis, alopecia areata, alopecia senilis, anerythroplasia, ankylosing spondylitis, antiphospholipid antibody syndrome, aortitis syndrome, aplastic anemia, atopic dermatitis, autoimmune haemolytic anemia, autoimmune hepatitis, autoimmune oophoritis, Balo disease, Basedow's disease, Behcet's disease, bronchial asthma, Castleman's syndrome, celiac disease, Chagas disease, chronic inflammatory demyelinating polyneuropathy, Churg-Strauss syndrome, Cogans syndrome, comical cornea, comical leucoma, Coxsackie myocarditis, CREST disease, Crohn's disease, cutaneous eosinophilia, cutaneous T-cell lymphoma, dermatitis erythrema multiforme, dermatomyositis, Dressler's syndrome, dystrophia epithelialis corneae, eczematous dermatitis, eosinophilic fasciitis, eosinophilic gastroenteritis, epidermolysis bullosa, Evans syndrome, fibrosing alveolitis, gestational pemphigoid, glomerulonephritis, Goodpasture's syndrome, graft-versus-host disease, Graves' disease, Guillain-Barre Syndrome, Hashimoto's disease, haemolytic-uretic syndrome, herpetic keratitis, ichthyosis vulgaris, idiopathic interstitial pneumonia, idiopathic thrombocytopenic purpura, inflammatory bowel diseases, Kawasaki's disease, keratitis, keratoconjunctivitis, Lambert-Eaton syndrome, leukoderma vulgaris, lichen planus, lichen sclerosus, Lyme disease, linear IgA disease, megaloblastic anemia, Meniere's disease, Mooren's ulcer, Mucha-Habermann disease, multiple myositis, multiple sclerosis, myasthenia gravis,

72. A method according to claim 71 wherein the disorder is selected from the group consisting of ankylosing spondylitis, Graves' disease, inflammatory bowel diseases (Crohn's disease, ulcerative colitis), multiple sclerosis, psoriasis and rheumatoid arthritis.

73. A method according to claim 65 wherein the protein tyrosine kinase is a Group XIV protein tyrosine kinase.

74. A method according to claim 73 wherein the Group XIV protein tyrosine kinase is selected from the group consisting of PDGFR-b, PDGFR-a, CSF1R, c-kit, Flk2, FLT1, FLT2, FLT3 and FLT4 or a functional equivalent thereof.

75. A method according to claim 74 wherein the Group XIV protein tyrosine kinase is FLT3 or a functional equivalent thereof.

76. A method according to claim 75 wherein the FLT3 includes an internal tandem duplication.

77. A method according to claim 76 wherein the internal tandem duplication is a duplication of amino acids VDFREYEYDH at position 592-601.

78. A method according to any one of claims 73 to 77 wherein the condition is selected from the group consisting of acute myeloid leukaemia, acute promyelocytic leukaemia, acute lymphocytic leukaemia, myelodysplastic syndromes, leukocytosis, juvenile myelomonocytic leukaemia, acute B-cell leukaemia, chronic myeloid leukaemia,
acute T-cell leukaemia, myeloproliferative disorders, and chronic myelomonocytic leukaemia.

79. A method according to claim 59 wherein the one or more protein kinase(s) include at least two kinases selected from the group consisting of CDK2, FLT3 and JAK2 or functional equivalents thereof.

80. A method according to claim 79 wherein the one or more protein kinase(s) include all three of CDK2, FLT3 and JAK2 or functional equivalents thereof.

81. Use of a compound according to any one of claims 1 to 22 in the preparation of a medicament for treating a condition in an animal in which inhibition of one or more protein kinase(s) can prevent, inhibit or ameliorate the pathology or symptomology of the condition.

82. A use according to claim 81 wherein the one or more protein kinase(s) is a cyclin-dependent protein kinase.

83. A use according to claim 82 wherein the cyclin-dependent kinase is a Group I CMCG kinase.

84. A use according to claim 83 wherein the Group I CMCG kinase is selected from the group consisting of CDC2Hs, CDK2, CDK3, CDK4, CDK5, CDK6, CDK9, PCTAIRE1, PCTAIRE2, PCTAIRE3, CAK/MO15, Dm2, Dm2c, Ddc2, DdPRK, LmmCRKI, PIC2R, EhC2R, CICdc2R, cdc2+, CDC28, PHO85, KIN28, FpCdc2, MsCdc2B, and OsC2R or a functional equivalent thereof.

85. A use according to claim 83 or 84 wherein the Group I CMCG kinase is CDK2 or a functional equivalent thereof.

86. A use according to any one of claims 82 to 85 wherein the condition is selected from the group consisting of prostate cancer, retinoblastoma, malignant neoplasm of breast, malignant tumour of colon, endometrial hyperplasia, osteosarcoma, squamous cell carcinoma, non-small cell lung cancer, melanoma, liver cell carcinoma, malignant neoplasm of pancreas, myeloid leukemia, cervical carcinoma, fibroid tumour, adenocarcinoma of the colon, T-cell leukemia, glioma, glioblastoma, oligodendroglioma,
lymphoma, ovarian cancer, restenosis, astrocytoma, bladder neoplasms, musculoskeletal neoplasms and Alzheimer's Disease.

87. A use according to claim 81 wherein the one or more protein kinase(s) is a protein tyrosine kinase.

88. A use according to claim 87 wherein the protein tyrosine kinase is a Group VII protein tyrosine kinase.

89. A use according to claim 88 wherein the Group VII protein tyrosine kinase is selected from the group consisting of TYK2, JAK1, JAK2 and HOP or a functional equivalent thereof.

90. A use according to claim 89 wherein the Group VII protein tyrosine kinase is JAK2 or a functional equivalent thereof.

91. A use according to claim 90 wherein the JAK2 includes a V to F mutation at position 617.

92. A use according to any one of claims 88 to 91 wherein the condition is selected from the group consisting of Myeloproliferative disorders (chronic idiopathic myelofibrosis, polycythemia vera, essential thrombocythemia, chronic myeloid leukemia), myeloid metaplasia, chronic myelomonocytic leukemia, acute lymphocytic leukemia, acute erythroblastic leukemia, Hodgkin's disease, B-cell lymphoma, acute T-cell leukemia, breast carcinoma, ovarian cancer, colon carcinoma, prostate cancer, melanoma, myelodysplastic syndromes, keloids, congestive heart failure, ischemia, thrombosis, cardiac hypertrophy, pulmonary hypertension, and retinal degeneration.

93. A use according to any one of claims 88 to 91 wherein the condition is an inflammatory disorder or an autoimmune disorder selected from the group consisting of acute disseminated encephalomyelitis, Addison's disease, agammaglobulinemia, agranulocytosis, allergic asthma, allergic encephalomyelitis, allergic rhinitis, alopecia areata, alopecia senilis, anerythroplasia, ankylosing spondylitis, antiphospholipid antibody syndrome, aortitis syndrome, aplastic anemia, atopic dermatitis, autoimmune haemolytic anemia, autoimmune hepatitis, autoimmune oophoritis, Balo disease, Basedow's disease, Behcet's disease, bronchial asthma, Castleman's syndrome, celiac disease, Chagas

94. A use according to claim 93 wherein the disorder is selected from the group consisting of ankylosing spondylitis, Graves' disease, inflammatory bowel diseases (Crohn's disease, ulcerative colitis), multiple sclerosis, psoriasis and rheumatoid arthritis...

95. A use according to claim 87 wherein the protein tyrosine kinase is a Group XIV protein tyrosine kinase.

96. A use according to claim 95 wherein the Group XIV protein tyrosine kinase is selected from the group consisting of PDGFR-b, PDGFR-a, CSF1R, c-kit, Flk2, FLT1, FLT2, FLT3 and FLT4 or a functional equivalent thereof.
97. A use according to claim 96 wherein the Group XIV protein tyrosine kinase is FLT3 or a functional equivalent thereof.

98. A use according to claim 97 wherein the FLT3 includes an internal tandem duplication.

99. A use according to claim 98 wherein the internal tandem duplication is a duplication of amino acids VDFREYEYDH at position 592-601.

100. A use according to any one of claims 95 to 99 wherein the condition is selected from the group consisting of acute myeloid leukaemia, acute promyelocytic leukaemia, acute lymphocytic leukaemia, myelodysplastic syndromes, leukocytosis, juvenile myelomonocytic leukaemia, acute B-cell leukaemia, chronic myeloid leukaemia, acute T-cell leukaemia, myeloproliferative disorders, and chronic myelomonocytic leukaemia.

101. A use according to claim 81 wherein the one or more protein kinase(s) include at least two kinases selected from the group consisting of CDK2, FLT3 and JAK2 or functional equivalents thereof.

102. A use according to claim 101 wherein the one or more protein kinase(s) include all three of CDK2, FLT3 and JAK2 or functional equivalents thereof.

103. Use of a compound according to any one of claims 1 to 22 in the preparation of a medicament for the treatment or prevention of a kinase-related disorder.

104. A use according to claim 103 wherein the kinase-related disorder is a proliferative disorder.

105. A use according to claim 104 wherein the proliferative disorder is elected from the group consisting of myeloproliferative disorders (chronic idiopathic myelofibrosis, polycythaemia vera, essential thrombocythaemia, chronic myeloid leukaemia), myeloid metaplasia, chronic myelomonocytic leukaemia, acute myeloid leukaemia, juvenile myelomonocytic leukaemia, acute promyelocytic leukaemia, acute lymphocytic leukaemia, acute erythoblastic leukaemia, acute B-cell leukaemia, leukocytosis, Hodgkin's disease, B-cell lymphoma, acute T-cell leukaemia, breast carcinoma, ovarian cancer, colon carcinoma, prostate cancer, melanoma, myelodysplastic syndromes, keloids,
retinoblastoma, malignant neoplasm of breast, malignant tumour of colon, endometrial hyperplasia, osteosarcoma, squamous cell carcinoma, non-small cell lung cancer, melanoma, liver cell carcinoma, malignant neoplasm of pancreas, myeloid leukaemia, cervical carcinoma, fibroid tumour, adenocarcinoma of the colon, glioma, glioblastoma, oligodendroglioma, lymphoma, ovarian cancer, restenosis, astrocytoma, bladder neoplasms, and musculoskeletal neoplasms.

106. A use according to claim 105 where the proliferative disorder is a myeloproliferative disorder.

107. A use according to claim 106 wherein the myeloproliferative disorder is selected from the group consisting of polycythemia vera, essential thrombocythemia and idiopathic myelofibrosis.

108. A use according to claim 104 wherein the proliferative disorder is cancer.

109. A use according to claim 108 wherein the cancer is a solid tumour.

110. A use according to claim 109 wherein the solid tumour is a tumour present in or metastasized from an organ or tissue selected from the group consisting of breast, ovary, colon, prostate, endometrium, bone, skin, lung, liver, pancreas, cervix, brain, neural tissue, lymphatic tissue, blood vessel, bladder and muscle.

111. A use according to claim 108 wherein the cancer is a haematological cancer.

112. A use according to claim 111 wherein the haematological cancer is selected from the group consisting of acute myeloid leukaemia, acute promyelocytic leukaemia, acute lymphocytic leukaemia, myelodysplastic syndrome, leukocytosis, juvenile myelomonocytic leukaemia, acute B-cell leukaemia, chronic myeloid leukaemia, acute T-cell leukaemia, chronic myelomonocytic leukaemia, myeloid metaplasia, chronic myelomonocytic leukaemia, acute erythroblastic leukaemia, Hodgkin's disease, and B-cell lymphoma.

113. A use according to claim 103 wherein the condition is an inflammatory disorder or an autoimmune disorder selected from the group consisting of acute disseminated encephalomyelitis, Addison's disease, agammaglobulinemia, agranulocytosis, allergic asthma, allergic encephalomyelitis, allergic rhinitis, alopecia areata, alopecia senilis, anerythroplasia, ankyllosing spondylitis, antiphospholipid antibody syndrome, aortitis

114. A use according to claim 113 wherein the disorder is selected from the group consisting of ankylosing spondylitis, Graves' disease, inflammatory bowel diseases (Crohn's disease, ulcerative colitis), multiple sclerosis, psoriasis and rheumatoid arthritis...

115. A use according to claim 103 wherein the kinase-related disorder is a cardiovascular disorder.
116. A use according to claim 115 wherein the cardiovascular disorder is selected from the group consisting of congestive heart failure, ischemia, thrombosis, cardiac hypertrophy and restenosis.

117. A use according to claim 103 wherein the kinase-related disorder is a neurodegenerative disorder.

118. A use according to claim 117 wherein the neurodegenerative disorder is Alzheimer's disease.

119. A method of treating or preventing a kinase-related disorder including administration of a therapeutically effective amount of a compound according to any one of claims 1 to 22 to a patient in need thereof.

120. A method according to claim 119 wherein the kinase-related disorder is a proliferative disorder.

121. A method according to claim 120 wherein the proliferative disorder is selected from the group consisting of myeloproliferative disorders (chronic idiopathic myelofibrosis, polycythemia vera, essential thrombocythemia, chronic myeloid leukaemia), myeloid metaplasia, chronic myelomonocytic leukaemia, acute myeloid leukaemia, juvenile myelomonocytic leukaemia, acute promyelocytic leukaemia, acute lymphocytic leukaemia, acute erythroid leukaemia, acute B-cell leukaemia, leukocytosis, Hodgkin's disease, B-cell lymphoma, acute T-cell leukaemia, breast carcinoma, ovarian cancer, colon carcinoma, prostate cancer, melanoma, myelodysplastic syndromes, keloids, retinoblastoma, malignant neoplasm of breast, malignant tumour of colon, endometrial hyperplasia, osteosarcoma, squamous cell carcinoma, non-small cell lung cancer, melanoma, liver cell carcinoma, malignant neoplasm of pancreas, myeloid leukaemia, cervical carcinoma, fibroid tumour, adenocarcinoma of the colon, glioma, glioblastoma, oligodendroglioma, lymphoma, ovarian cancer, restenosis, astrocytoma, bladder neoplasms, and musculoskeletal neoplasms.

122. A method according to claim 120 where the proliferative disorder is a myeloproliferative disorder.
123. A method according to claim 122 wherein the myeloproliferative disorder is selected from the group consisting of polycythemia vera, essential thrombocythemia, and idiopathic myelofibrosis.

124. A method according to claim 120 wherein the proliferative disorder is cancer.

125. A method according to claim 124 wherein the cancer is a solid tumour.

126. A method according to claim 125 wherein the solid tumour is a tumour present in or metastasized from an organ or tissue selected from the group consisting of breast, ovary, colon, prostate, endometrium, bone, skin, lung, liver, pancreas, cervix, brain, neural tissue, lymphatic tissue, blood vessel, bladder and muscle.

127. A method according to claim 124 wherein the cancer is a haematological cancer.

128. A method according to claim 127 wherein the haematological cancer is selected from the group consisting of acute myeloid leukaemia, acute promyelocytic leukaemia, acute lymphocytic leukaemia, myelodysplastic syndrome, leukocytosis, juvenile myelomonocytic leukaemia, acute B-cell leukaemia, chronic myeloid leukaemia, acute T-cell leukaemia, chronic myelomonocytic leukaemia, myeloid metaplasia, chronic myelomonocytic leukaemia, acute erythroblastic leukaemia, Hodgkin's disease, and B-cell lymphoma.

129. A method according to claim 119 wherein the kinase related disorder is an inflammatory disorder or an autoimmune disorder selected from the group consisting of acute disseminated encephalomyelitis, Addison's disease, agammaglobulinemia, agranulocytosis, allergic asthma, allergic encephalomyelitis, allergic rhinitis, alopecia areata, alopecia senilis, anerythroplasia, ankylosing spondylitis, antiphospholipid antibody syndrome, aortitis syndrome, aplastic anemia, atopic dermatitis, autoimmune haemolytic anemia, autoimmune hepatitis, autoimmune oophoritis, Balo disease, Basedow's disease, Behcet's disease, bronchial asthma, Castleman's syndrome, celiac disease, Chagas disease, chronic inflammatory demyelinating polyneuropathy, Churg-Strauss syndrome, Cogans syndrome, comical cornea, comical leukemia, Coxsackie myocarditis, CREST disease, Crohn's disease, cutaneous eosinophilia, cutaneous T-cell lymphoma, dermatitis erythema multiforme, dermatomyositis, Dressler's syndrome, dystrophia epithelialis corneae, eczematous dermatitis, eosinophilic fasciitis, eosinophilic gastroenteritis, epidermolysis bullosa, Evans syndrome, fibrosing alveolitis, gestational pemphigoid,

130. A method according to claim 129 wherein the disorder is selected from the group consisting of ankylosing spondylitis, Graves' disease, inflammatory bowel diseases (Crohn's disease, ulcerative colitis), multiple sclerosis, psoriasis and rheumatoid arthritis...

131. A method according to claim 119 wherein the kinase-related disorder is a cardiovascular disorder.

132. A method according to claim 131 wherein the cardiovascular disorder is selected from the group consisting of congestive heart failure, ischemia, thrombosis, cardiac hypertrophy and restenosis.

133. A method according to claim 119 wherein the kinase-related disorder is a neurodegenerative disorder.

134. A method according to claim 133 wherein the neurodegenerative disorder is Alzheimer's disease.
135. Use of a compound according to any one of claims 1 to 22 in the treatment of a proliferative disorder.

136. A use according to claim 135 wherein the proliferative disorder is selected from the group consisting of wherein the proliferative disorder is elected from the group consisting of myeloproliferative disorders (chronic idiopathic myelofibrosis, polycythemia vera, essential thrombocythemia, chronic myeloid leukaemia), myeloid metaplasia, chronic myelomonocytic leukaemia, acute myeloid leukaemia, juvenile myelomonocytic leukaemia, acute promyelocytic leukaemia, acute lymphocytic leukaemia, acute erythroblastic leukaemia, acute B-cell leukaemia, leukocytosis, Hodgkin's disease, B-cell lymphoma, acute T-cell leukaemia, breast carcinoma, ovarian cancer, colon carcinoma, prostate cancer, melanoma, myelodysplastic syndromes, keloids, retinoblastoma, malignant neoplasm of breast, malignant tumour of colon, endometrial hyperplasia, osteosarcoma, squamous cell carcinoma, non-small cell lung cancer, melanoma, liver cell carcinoma, malignant neoplasm of pancreas, myeloid leukaemia, cervical carcinoma, fibroid tumour, adenocarcinoma of the colon, glioma, glioblastoma, oligodendrogloma, lymphoma, ovarian cancer, restenosis, astrocytoma, bladder neoplasms, and musculoskeletal neoplasms.

137. A use according to claim 135 where the proliferative disorder is a myeloproliferative disorder.

138. A use according to claim 137 wherein the myeloproliferative disorder is selected from the group consisting of polycythemia vera, essential thrombocythemia, and idiopathic myelofibrosis.

139. A use according to claim 135 wherein the proliferative disorder is cancer.

140. A use according to claim 139 wherein the cancer is a solid tumour.

141. A use according to claim 140 wherein the solid tumour is a tumour present in or metastasized from an organ or tissue selected from the group consisting of breast, ovary, colon, prostate, endometrium, bone, skin, lung, liver, pancreas, cervix, brain, neural tissue, lymphatic tissue, blood vessel, bladder and muscle.

142. A use according to claim 139 wherein the cancer is a haematological cancer.
143. A use according to claim 142 wherein the haematological cancer is selected from the group consisting of acute myeloid leukaemia, acute promyelocytic leukaemia, acute lymphocytic leukaemia, myelodysplastic syndrome, leukocytosis, juvenile myelomonocytic leukaemia, acute B-cell leukaemia, chronic myeloid leukaemia, acute T-cell leukaemia, chronic myelomonocytic leukaemia, myeloid metaplasia, chronic myelomonocytic leukaemia, acute erythroid leukaemia, Hodgkin’s disease, and B-cell lymphoma.