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

(57) Abstract: This invention relates to novel compounds having the formula (I), and to their pharmaceutical compositions and to their methods of use. These novel compounds provide a treatment for cancer.

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PYRAZOLYL-AMINO- SUBSTITUTED PYRIMIDINES AND THEIR USE IN THE TREATMENT OF CANCER

Field of the invention

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

Background of the invention

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

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

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

In the past decade, a considerable number of literature documentations linking Trk signalling with cancer have published. For example, while Trk's are expressed at low levels outside the nervous system in the adult, Trk expression is increased in late stage prostate cancers. Both normal prostate tissue and androgen- dependent prostate tumours express low levels of Trk A and undetectable levels of Trk B and C. However, all isoforms of Trk receptors as well as their cognate ligands are up-regulated in late stage, androgen-independent prostate cancer. There is additional evidence that these late stage prostate cancer

cells become dependent on the Trk/neurotrophin axis for their survival. Therefore, Trk inhibitors may yield a class of apoptosis-inducing agents specific for androgen- independent prostate cancer (Weeraratna, A. T. et al *The Prostate*, 2000, 45, I40-I48).

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

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

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

Summary of the invention

In accordance with the present invention, the applicants have hereby discovered novel pyrazole compounds, or pharmaceutically acceptable salts thereof, which possess Trk kinase inhibitory activity and are accordingly useful for their anti-proliferation and/or proapoptotic (such as anti-cancer) activity and in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said pyrazole compounds, or pharmaceutically acceptable salts thereof, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments for use in the production of an anti-proliferation and/or proapoptotic effect in warm-blooded animals such as man.

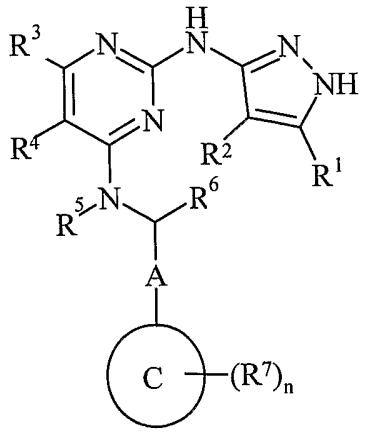
Also in accordance with the present invention the applicants provide methods of using such pyrazole compounds, or pharmaceutically acceptable salts thereof, in the treatment of cancer.

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

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

Detailed description of the invention

Accordingly, the present invention provides a compound of formula **(I)**:



(I)

wherein:

$\mathbf{R^1}$ and $\mathbf{R^2}$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino,

N,N-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R^1 and R^2 independently of each other may be optionally substituted on carbon by one or more R^8; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^3 and **R^4** are independently selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R^3 and R^4 independently of each other may be optionally substituted on carbon by one or more R^{10}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{11};

or **R^3** and **R^4** together with the pyrimidine bond to which they are attached form a 5 or 6 membered carbocyclic ring or a 5 or 6 membered heterocyclic ring wherein said ring is fused to the pyrimidine of formula **(I)**; wherein the double bonds of the resulting bicyclic ring may be further delocalised across the whole of the bicyclic ring; and wherein said carbocyclic ring or heterocyclic ring may be optionally substituted on carbon by one or more R^{12}; and wherein if said heterocyclic ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

R^5 is hydrogen or optionally substituted C_{1-6}alkyl; wherein said optional substituents are selected from one or more R^{14};

R^6 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R^6 may be optionally substituted on carbon by one or more R^{15}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{16};

A is a direct bond or C_{1-2}alkylene; wherein said C_{1-2}alkylene may be optionally substituted by one or more R^{17};

Ring C is carbocyclyl or heterocyclyl;

$\mathbf{R^7}$ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R^7 may be optionally substituted on carbon by one or more R^{18}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{19};

n = 0, 1, 2 or 3; wherein the values of R^7 may be the same or different;

$\mathbf{R^8}$, $\mathbf{R^{10}}$, $\mathbf{R^{12}}$, $\mathbf{R^{14}}$, $\mathbf{R^{15}}$, $\mathbf{R^{17}}$ and $\mathbf{R^{18}}$ are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R^8, R^{10}, R^{12}, R^{14}, R^{15}, R^{17} and R^{18} independently of each other may be optionally substituted on carbon by one or more R^{20}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{21};

$\mathbf{R^9}$, $\mathbf{R^{11}}$, $\mathbf{R^{13}}$, $\mathbf{R^{16}}$, $\mathbf{R^{19}}$ and $\mathbf{R^{21}}$ are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; wherein R^9, R^{11}, R^{13}, R^{16}, R^{19} and R^{21} independently of each other may be optionally substituted on carbon by on or more R^{22};

$\mathbf{R^{20}}$ and $\mathbf{R^{22}}$ are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl,

N-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R^{20} and R^{22} independently of each other may be optionally substituted on carbon by one or more R^{23}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{24};

R^{23} is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl; and

R^{24} is selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

or a pharmaceutically acceptable salt thereof.

Particular values of the variable groups contained in formula **(I)** are as follows. Such values may be used, where appropriate, with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

R^1 is hydrogen.

R^1 is selected from C_{1-6}alkyl, C_{1-6}alkoxy or carbocyclyl

R^1 is selected from methyl, methoxy or cyclopropyl.

R^2 is selected from C_{1-6}alkyl, C_{1-6}alkoxy or carbocyclyl

R^2 is selected from methyl, methoxy or cyclopropyl.

R^2 is hydrogen.

R^1 and R^2 are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy or carbocyclyl.

R^1 and R^2 are independently selected from hydrogen, methyl, methoxy or cyclopropyl.

R^1 is hydrogen and R^2 is selected from methyl, methoxy or cyclopropyl.

R^3 is hydrogen.

R^4 is selected from hydrogen, halo, cyano and C_{1-6}alkyl; wherein R^3 and R^4 independently of each other may be optionally substituted on carbon by one or more R^{10}; wherein R^{10} is halo.

R^4 is selected from hydrogen, chloro, cyano and methyl; wherein R^4 may be optionally substituted on carbon by one or more R^{10}; wherein R^{10} is fluoro.

R^4 is selected from hydrogen, chloro, cyano, trifluoromethyl and methyl.

R^3 and R^4 are independently selected from hydrogen, halo, cyano and C_{1-6}alkyl; wherein R^3 and R^4 independently of each other may be optionally substituted on carbon by one or more R^{10}; wherein R^{10} is halo.

R^3 and R^4 are independently selected from hydrogen, chloro, cyano and methyl; wherein R^3 and R^4 independently of each other may be optionally substituted on carbon by one or more R^{10}; wherein R^{10} is fluoro.

R^3 and R^4 are independently selected from hydrogen, chloro, cyano, trifluoromethyl and methyl.

R^3 is hydrogen and R^4 is selected from hydrogen, halo, cyano and C_{1-6}alkyl; wherein R^3 and R^4 independently of each other may be optionally substituted on carbon by one or more R^{10}; wherein R^{10} is halo.

R^3 is hydrogen and R^4 is selected from hydrogen, chloro, cyano and methyl; wherein R^4 may be optionally substituted on carbon by one or more R^{10}; wherein R^{10} is fluoro.

R^3 is hydrogen and R^4 is selected from hydrogen, chloro, cyano, trifluoromethyl and methyl.

R^5 is hydrogen.

R^5 is optionally substituted C_{1-6}alkyl; wherein said optional substituents are selected from one or more R^{14}.

R^6 is C_{1-6}alkyl; wherein R^6 may be optionally substituted on carbon by one or more R^{15}; wherein R^{15} is hydroxy.

R^6 is methyl; wherein R^6 may be optionally substituted on carbon by one or more R^{15}; wherein R^{15} is hydroxy.

R^6 is methyl or hydroxymethyl.

A is a direct bond.

A is C_{1-2}alkylene; wherein said C_{1-2}alkylene may be optionally substituted by one or more R^{17}.

Ring C is carbocyclyl.

Ring C is phenyl.

Ring C is heterocyclyl.

R^7 is halo.

R^7 is fluoro.

n = 0 or 1.

n = 0.

n = 1.

Therefore in a further aspect of the invention there is provided a compound of formula **(I)** (as depicted herein above) wherein:

R^1 and R^2 are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy or carbocyclyl;

R^3 and R^4 are independently selected from hydrogen, halo, cyano and C_{1-6}alkyl; wherein R^3 and R^4 independently of each other may be optionally substituted on carbon by one or more R^{10};

R^5 is hydrogen;

R^6 is C_{1-6}alkyl; wherein R^6 may be optionally substituted on carbon by one or more R^{15};

A is a direct bond;

Ring C is carbocyclyl;

R^7 is halo;

n = 0 or 1;

R^{10} is halo;

R^{15} is hydroxy;

or a pharmaceutically acceptable salt thereof.

Therefore in a further aspect of the invention there is provided a compound of formula **(I)** (as depicted herein above) wherein:

R^1 is hydrogen;

R^2 is selected from methyl, methoxy or cyclopropyl;

R^3 is hydrogen;

R^4 is selected from hydrogen, chloro, cyano, trifluoromethyl and methyl;

R^5 is hydrogen;

R^6 is methyl or hydroxymethyl;

A is a direct bond;

Ring C is phenyl;

R^7 is fluoro;

n = 0 or 1;

or a pharmaceutically acceptable salt thereof.

Therefore in a further aspect of the invention there is provided a compound of formula **(I)** (as depicted herein above) wherein:

R^1 is selected from methyl, methoxy or cyclopropyl;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is selected from hydrogen, chloro, cyano, trifluoromethyl and methyl;

R^5 is hydrogen;

R^6 is methyl or hydroxymethyl;

A is a direct bond;

Ring C is phenyl;

R^7 is fluoro;

n = 0 or 1;

or a pharmaceutically acceptable salt thereof.

In another aspect of the invention, preferred compounds of the invention are any one of the Examples or a pharmaceutically acceptable salt thereof.

In an additional embodiment the present invention provides a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, for use as a medicament.

In an additional embodiment the present invention provides a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for use in the inhibition of Trk activity.

In an additional embodiment the present invention provides a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for use in the treatment or prophylaxis of cancer.

In an additional embodiment the present invention provides a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for use in the treatment of cancer in a warm-blooded animal such as man.

In an additional embodiment the present invention provides a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for use in the treatment or prophylaxis of cancers (solid tumors and leukemia), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial

restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation in a warm-blooded animal such as man.

In an additional embodiment the present invention provides a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for use in the production of an anti-proliferative effect.

In an additional embodiment the present invention provides a method of inhibiting Trk activity comprising administering to a host in need of such treatment a therapeutically effective amount of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof.

In an additional embodiment the present invention provides a method for the treatment of cancer comprising administering to a host in need of such treatment a therapeutically effective amount of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof.

In an additional embodiment the present invention provides a method for the treatment or prophylaxis of cancer comprising administering a therapeutically effective amount of a compound of formula **(I)** or a pharmaceutically acceptable salt thereof.

In an additional embodiment the present invention provides a method for the treatment or prophylaxis of cancers (solid tumors and leukemia), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation in a warm-blooded animal such as man comprising administering a therapeutically effective amount of a compound of formula **(I)** or a pharmaceutically acceptable salt thereof.

In an additional embodiment the present invention provides a method of producing an anti-proliferative effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof.

In an additional embodiment the present invention provides a pharmaceutical composition comprising a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, diluent or excipient.

In an additional embodiment the present invention provides a pharmaceutical composition comprising a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, diluent or excipient for use in the inhibition of Trk activity.

In an additional embodiment the present invention provides a pharmaceutical composition comprising a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, diluent or excipient for use in the treatment of cancer.

In an additional embodiment the present invention provides a pharmaceutical composition comprising a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, diluent or excipient for use in the treatment or prophylaxis of cancer.

In an additional embodiment the present invention provides a pharmaceutical composition comprising a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, diluent or excipient for use in the treatment or prophylaxis of cancers (solid tumors and leukemia), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

In an additional embodiment the present invention provides a pharmaceutical composition comprising a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, diluent or excipient for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

In an additional embodiment the present invention provides a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the inhibition of Trk activity.

In an additional embodiment the present invention provides a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of cancer.

In an additional embodiment the present invention provides a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a warm-blooded animal such as man.

In an additional embodiment the present invention provides a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of cancers (solid tumours and leukaemia), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and

chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation in a warm-blooded animal such as man.

In an additional embodiment the present invention provides a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the production of an anti-proliferative effect.

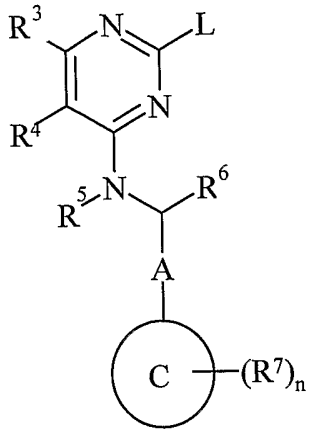
In one embodiment where the inhibition of Trk activity is referred to particularly this refers to the inhibition of Trk A activity.

In another embodiment where the inhibition of Trk activity is referred to particularly this refers to the inhibition of Trk B activity.

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

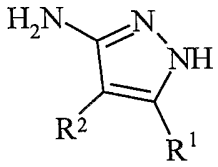
In a further aspect of the present invention provides a process for preparing a compound of formula **(I)** or a pharmaceutically acceptable salt thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula **(I)**) comprises of:

Process a) reaction of a pyrimidine of formula **(II)**:



(II)

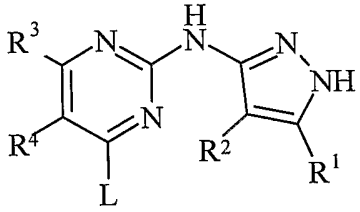
wherein L is a displaceable group; with an pyrazole amine of formula **(III)**:



(III)

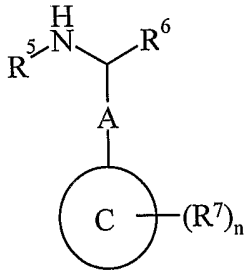
or

Process b) reacting a pyrimidine of formula **(IV)**:



(IV)

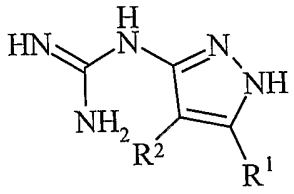
wherein L is a displaceable group; with a compound of formula **(V)**:



(V)

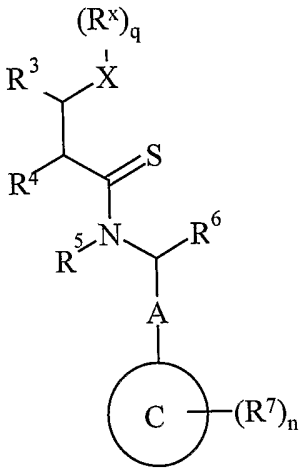
or

Process c) reacting a compound of formula **(VI)**:



(VI)

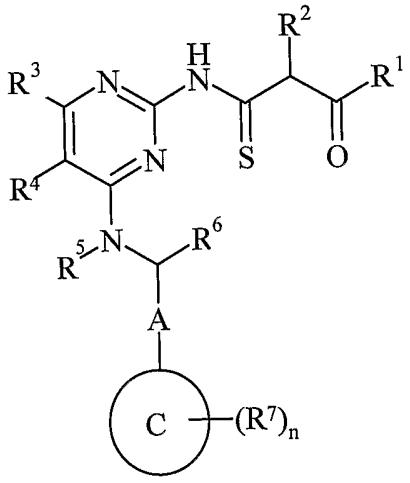
with a compound of formula **(VII)**:



(VII)

wherein X is an oxygen atom and q is 1; or X is a nitrogen atom and q is 2; and wherein each R^x independently represents a C_{1-6}alkyl group; or

Process d) reacting a compound of formula **(VIII)**:



(VIII)

with hydrazine;

and thereafter if necessary:

i) converting a compound of the formula **(I)** into another compound of the formula **(I)**;

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt.

L is a displaceable group, suitable values for L are for example, a halo or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group.

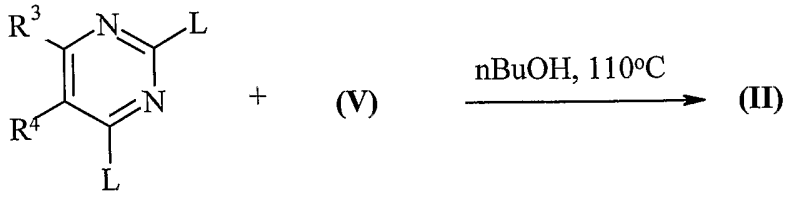
Specific reaction conditions for the above reactions are as follows.

Process a) Pyrimidines of formula **(II)** and pyrazole amine of formula **(III)** may be reacted together:

a) in the presence of a suitable solvent for example a ketone such as acetone or an alcohol such as ethanol or butanol or an aromatic hydrocarbon such as toluene or *N*-methyl pyrrolid-2-one, optionally in the presence of a suitable acid for example an inorganic acid such as hydrochloric acid or sulphuric acid, or an organic acid such as acetic acid or formic acid (or a suitable Lewis acid) and at a temperature in the range from 0°C to reflux, particularly reflux; or

b) under standard Buchwald conditions (for example see *J. Am. Chem. Soc.*, **118**, 7215; *J. Am. Chem. Soc.*, **119**, 8451; *J. Org. Chem.*, **62**, 1568 and 6066) for example in the presence of palladium acetate, in a suitable solvent for example an aromatic solvent such as toluene, benzene or xylene, with a suitable base for example an inorganic base such as caesium carbonate or an organic base such as potassium-*t*-butoxide, in the presence of a suitable ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and at a temperature in the range from 25 to 80°C.

Pyrimidines of the formula **(II)** may be prepared according to *Scheme 1*:



(IIa)

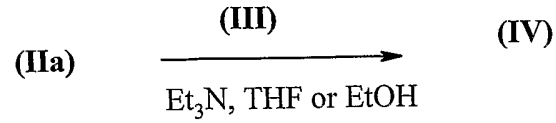
Scheme 1

wherein L is a displaceable group as defined herein above.

Pyrazole amines of formula **(III)** and compounds of formula **(IIa)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process b) Compounds of formula **(IV)** and formula **(V)** may be reacted together under the same conditions as outlined in *Process a)*.

Compounds of the formula **(IV)** may be prepared according to *Scheme 2*:

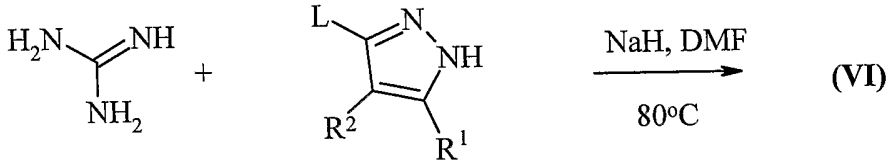


Scheme 2

Compounds of the formula **(V)** are commercially available compounds, or they are known in the literature, or they are prepared by standrd processes known in the art.

Process c) may conveniently be carried out in a suitable solvent such as *N*-methylpyrrolidinone or butanol at a temperature in the range from 100-200°C, in particular in the range from 150-170°C. The reaction is preferably conducted in the presence of a suitable base such as, for example, sodium methoxide or potassium carbonate.

Compounds of the formula **(VI)** may be prepared according to *Scheme 3*:

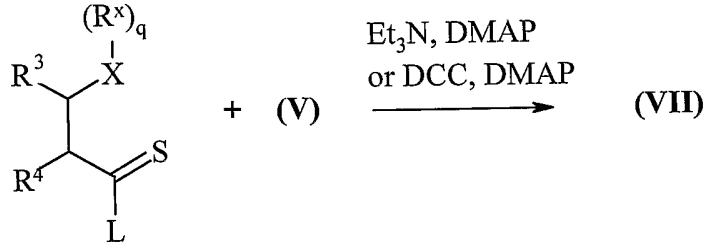


(VIa) **(VIb)**

Scheme 3

wherein L is a displaceable group as defined herein above.

Compounds of the formula **(VII)** may be prepared according to *Scheme 4*:



(VIIa)

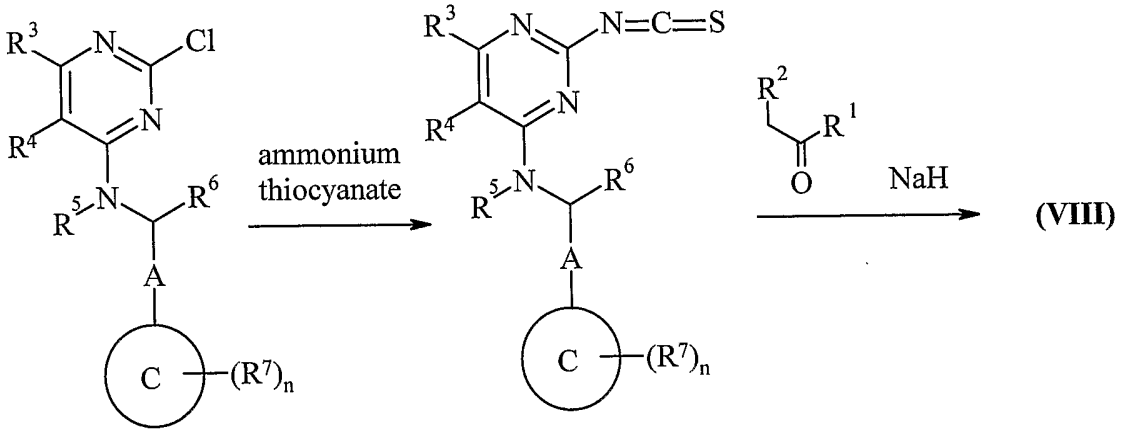
Scheme 4

wherein L is a displaceable group as defined herein above.

Compounds of the formula **(VIa)**, **(VIb)** and **(VIIa)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process d) may be carried out in a suitable solvent, for example, an alcohol such as ethanol or butanol at a temperature in the range from 50-120°C, in particular in the range from 70-100°C.

Compounds of the formula **(VIII)** may be prepared according to *Scheme 5*:



Scheme 5

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those

skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

Definitions

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example, "C_{1-6}alkyl" and "C_{1-4}alkyl" include methyl, ethyl, propyl, isopropyl and *t*-butyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight-chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched-chain version only. A similar convention applies to other radicals. The term "halo" refers to fluoro, chloro, bromo and iodo.

Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

A "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 4-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH_2- group can optionally be replaced by a -C(O)-, and a ring sulphur atom may be optionally oxidised to form the S-oxides. Examples and suitable values of the term "heterocyclyl" are morpholino, piperidyl, pyridyl, pyranyl, pyrrolyl, isothiazolyl, indolyl, quinolyl, thienyl, 1,3-benzodioxolyl, thiadiazolyl, piperazinyl, thiazolidinyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, tetrahydropyranyl, imidazolyl, pyrimidyl, pyrazinyl, pyridazinyl, isoxazolyl, *N*-methylpyrrolyl, 4-pyridone, 1-isoquinolone, 2-pyrrolidone, 4-thiazolidone, pyridine-*N*-oxide and quinoline-*N*-oxide. Further examples and suitable values of the term "heterocyclyl" are morpholino, piperazinyl and pyrrolidinyl. In one aspect of the invention a "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, it may, unless otherwise specified, be carbon or nitrogen linked, a -CH_2- group can optionally be replaced by a -C(O)-and a ring sulphur atom may be optionally oxidised to form the S-oxides.

A "carbocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms; wherein a -CH_2- group can optionally be replaced by a -C(O)-. Particularly "carbocyclyl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "carbocyclyl" include cyclopropyl,

cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl, naphthyl, tetralinyl, indanyl or 1-oxoindanyl.

The term "C_{m-n}" or "C_{m-n} group" used alone or as a prefix, refers to any group having m to n carbon atoms.

The term "optionally substituted" refers to either groups, structures, or molecules that are substituted and those that are not substituted.

An example of "C_{1-6}alkanoyloxy" is acetoxy. Examples of "C_{1-6}alkoxycarbonyl" include C_{1-4}alkoxycarbonyl, methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C_{1-6}alkoxy" include C_{1-4}alkoxy, C_{1-3}alkoxy, methoxy, ethoxy and propoxy. Examples of "C_{1-6}alkoxyimino" include C_{1-4}alkoxyimino, C_{1-3}alkoxyimino, methoxyimino, ethoxyimino and propoxyimino. Examples of "C_{1-6}alkanoylamino" include formamido, acetamido and propionylamino. Examples of "C_{1-6}alkyl$S(O)_a$ wherein a is 0 to 2" include C_{1-4}alkylsulphonyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C_{1-6}alkylthio" include methylthio and ethylthio. Examples of "C_{1-6}alkylsulphonylamino" include methylsulphonylamino and ethylsulphsulphonylamino. Examples of "C_{1-6}alkanoyl" include C_{1-4}alkanoyl, propionyl and acetyl. Examples of "*N*-(C_{1-6}alkyl)amino" include methylamino and ethylamino. Examples of "*N,N*-(C_{1-6}alkyl)$_2$amino" include di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino. Examples of "C_{2-6}alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C_{2-6}alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "*N*-(C_{1-6}alkyl)sulphamoyl" are *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-6}alkyl)$_2$sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-6}alkyl)carbamoyl" are *N*-(C_{1-4}alkyl)carbamoyl, methylaminocarbonyl and ethylaminocarbonyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$carbamoyl" are *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, dimethylaminocarbonyl and methylethylaminocarbonyl.

"RT" or "rt" means room temperature.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline

earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

It should be noted that the compounds claimed in this invention are capable of existing in different resonance structures and thus the compounds claimed herein include all possible resonance structures, for example optical isomers, diastereoisomers and geometric isomers and all tautomeric forms of the compounds of the formula **(I)**.

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

Formulations

Compounds of the present invention may be administered orally, parenteral, buccal, vaginal, rectal, inhalation, insufflation, sublingually, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level as the most appropriate for a particular patient.

An effective amount of a compound of the present invention for use in therapy of cancer is an amount sufficient to symptomatically relieve in a warm-blooded animal, particularly a human the symptoms of cancer, to slow the progression of cancer, or to reduce in patients with symptoms of cancer the risk of getting worse.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substance, which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having

the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify.

Suitable carriers include magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

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

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

In order to use a compound of the formula **(I)** or a pharmaceutically acceptable salt thereof for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

In addition to the compounds of the present invention, the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating one or more disease conditions referred to herein.

The term composition is intended to include the formulation of the active component or a pharmaceutically acceptable salt with a pharmaceutically acceptable carrier. For example this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols or nebulisers for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions.

Liquid form compositions include solutions, suspensions, and emulsions. Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

The pharmaceutical compositions can be in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparations, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

Combinations

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

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

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

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

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbb2 antibody trastuzumab [Herceptin™] and the anti-erbb1 antibody cetuximab [C225]) , farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and

6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin);

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

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

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

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies; and

(x) other treatment regimes including: dexamethasone, proteasome inhibitors (including bortezomib), isotretinoin (13-cis retinoic acid), thalidomide, revemid, Rituxamab, ALIMTA, Cephalon's kinase inhibitors CEP-701 and CEP-2563, anti-Trk or anti-NGF monoclonal antibodies, targeted radiation therapy with 131I-metaiodobenzylguanidine (131I-MIBG), anti-G(D2) monoclonal antibody therapy with or without granulocyte-macrophage colony-stimulating factor (GM-CSF) following chemotherapy.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products

employ the compounds of this invention, or pharmaceutically acceptable salts thereof, within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

Synthesis

The compounds, or pharmaceutically acceptable salts thereof, of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds, or pharmaceutically acceptable salts thereof, of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Such methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety by reference.

The novel compounds, or pharmaceutically acceptable salts thereof, of this invention may be prepared using the reactions and techniques described herein. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents, which are compatible with the reaction conditions, will be readily apparent to one skilled in the art and alternate methods must then be used.

Examples

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

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

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

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

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

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

(vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in part per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz in DMSO-d_6 unless otherwise stated;

(viii) chemical symbols have their usual meanings;

(ix) solvent ratio was given in volume : volume (v/v) terms.

(x) the following abbreviations have been used:

DCM	dichloromethane;
HPLC	high-performance liquid chromatography; and
DIPEA	N, N-diisopropylethylamine.

Example 1

(2R)-2-({5-Chloro-2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]pyrimidin-4-yl}amino)-2-(4-fluorophenyl)ethanol

To a microwave vial (Personal Chemistry) was added (2R)-2-[(2,5-dichloropyrimidin-4-yl)amino]-2-(4-fluorophenyl)ethanol (Method 1, 250 mg, 0.83 mmol), 5-cyclopropyl-1*H*-pyrazol-3-amine (204 mg, 1.66 mmol), DIPEA (0.17 ml, 0.97 mmol) and n-butanol (2 ml). The reaction mixture was heated for 160°C for 5 hours. Solvent was removed. Semi-prep HPLC (Gilson) purification gave the title compound as a solid (43 mg, 13%). ^{1}H NMR (300 MHz, DMSO-*d6*) δ 0.76 (m, 2H), 0.97 (m, 2H), 1.87(m, 1H), 3.73-3.85 (m, 2H), 5.22 (m, 2H), 7.13 (m, 2H), 7.47 (m, 2H), 7.97 (d, 1H), 8.28 (s, 1H).

Example 2-8

Following a similar procedure to Example 1, the following compounds were synthesized via reaction of a suitable pyrimidine or quinazoline (method of production of which is also listed) and a suitable amine.

Ex.	Name	^{1}H NMR	SM1	SM2
2	(2R)-2-({2-[(5-Cyclopropyl-1H-pyrazol-3-yl)amino]pyrimidin-4-yl}amino)-2-(4-fluorophenyl)ethanol	(DMSO-d_6+D_2O): 0.63 (m, 2H), 0.93 (m, 2H), 1.82 (m, 1H), 3.67 (m, 2H), 4.98-5.17 (m, 1H), 5.61-5.70 (m, 1H), 6.30-6.62 (m, 1H), 7.09 (m, 2H), 7.32 (m, 2H), 7.68-7.86 (m, 1H)	Method 2	5-cyclopropyl-1H-pyrazol-3-amine
3	(2R)-2-{[2-[(5-Cyclopropyl-1H-pyrazol-3-yl)amino]-5-(trifluoromethyl) pyrimidin-4-yl]amino}-2-(4-fluorophenyl)ethanol	0.67 (m, 2H), 0.94 (m, 2H), 1.88 (m, 1H), 3.75 (m, 2H), 5.34 (m, 1H), 5.90 (s, 1H), 7.14 (m, 2H), 7.40 (m, 2H). 8.25 (s, 1H), 9.91 (br s, 1H)	Method 3	(2R)-2-amino-2-(4-fluorophenyl)ethanol
4	2-[(5-Cyclopropyl-1H-pyrazol-3-yl)amino]-4-{[(1S)-1-(4-fluorophenyl) ethyl]amino} pyrimidine-5-carbonitrile	0.63 (m, 2H), 0.92 (m, 2H), 1.51 (d, J = 6.8 Hz, 3H), 1.86 (m, 1H), 5.34 (br, 1H), 6.00 (br, 1H), 7.14 (m, 2H), 7.40 (br, 2H), 8.01 (br, 1H), 8.28 (s, 1H), 9.86 (br, 1H), 12.01 (s, 1H). MS: Calcd.: 363.4; Found: $[M+H]^+$ 364.2	Method 4	5-cyclopropyl-1H-pyrazol-3-amine
5	(2R)-2-({2-[(5-Cyclopropyl-1H-pyrazol-3-yl)amino]-5-methylpyrimidin-4-yl}amino)-2-(4-fluorophenyl)ethanol	0.69-0.77 (m, 2H), 0.96 (m, 2H), 1.87 (m, 1H), 2.21 (s, 3H), 3.70-3.87 (m, 2H), 5.16-5.20 (m, 2H), 7.14 (m, 2H), 7.40 (m, 2H). 7.95 (s, 1H), 8.42 (s, 1H)	Method 5	5-cyclopropyl-1H-pyrazol-3-amine
6	(2R)-2-({5-Chloro-2-[(5-isopropoxy-1H-pyrazol-3-yl)amino] pyrimidin-4-yl}amino)-2-(4-fluorophenyl)ethanol	1.28 (d, 6H), 3.73-3.85 (m, 2H), 4.81 (m, 1H), 4.86 (s, 1H), 5.12 (m, 1H), 7.10 (m, 2H), 7.46 (m, 2H). 7.81 (d, 1H), 8.19 (s, 1H)	Method 1	5-isopropoxy-1H-pyrazol-3-amine

Ex.	Name	^{1}H NMR	SM1	SM2
7	(2R)-2-({5-Chloro-2-[(5-methyl-1H-pyrazol-3-yl)amino] pyrimidin-4-yl} amino)-2-(4-fluorophenyl)ethanol	2.18 (s, 3H), 3.73-3.85 (m, 2H), 5.27 (m, 1H), 5.47 (s, 1H), 7.13 (m, 2H), 7.47 (m, 2H). 7.98 (d, 1H), 8.30 (s, 1H)	Method 1	5-methyl-1H-pyrazol-3-amine
8	N^2-(3-Cyclopropyl-1H-pyrazol-5-yl)-N^4-(1-phenylethyl)-5-(trifluoromethyl) pyrimidine-2,4-diamine	0.65 (m, 2H), 0.93 (m, 2H), 1.56 (m, 3H), 1.88 (m, 1H), 5.55 (m, 1H), 5.90 (s, 1H), 7.20 (m, 2H), 7.34 (m, 2H), 8.27 (s, 1H)	Method 6	5-cyclopropyl-1H-pyrazol-3-amine

Preparation of starting materials:

The starting materials for the Examples contained herein are either commercially available or are readily prepared by standard methods from known materials. For example the following reactions are illustrations but not limitations of the preparation of some of the starting materials and examples used herein.

Method 1

(2R)-2-[(2,5-Dichloropyrimidin-4-yl)amino]-2-(4-fluorophenyl)ethanol

To a solution of 2,4,5-trichloropyrimidine (1.00 g, 5.46 mmol), triethylamine (0.91 ml, 6.54 mmol) in ethanol (20 ml) was added (2*R*)-2-amino-2-(4-fluorophenyl)ethanol (847 mg, 5.46 mmol). The reaction mixture was stirred at room temperature for 12 hours. Solvent was removed. The mixture was separated between DCM and water. The combined organic layers were washed with brine and concentrated to give the desired product as a solid (1.59 g, 97%). ^{1}H NMR (300 MHz, DMSO-*d6*) δ 3.68-3.79 (m, 2H), 5.03 (m, 1H), 5.19 (m, 1H), 7.14 (m, 2H), 7.43 (m, 2H), 8.03 (d, 1H), 8.19 (s, 1H).

Method 2-6

The following compounds were prepared by the procedure of Method 1 using the appropriate starting materials.

Meth	Compound	NMR	Pyrimidine	Amine
2	(2*R*)-2-[(2-Chloropyrimidin-4-yl)amino]-2-(4-fluorophenyl) ethanol	3.61(m, 2H), 5.01 (m, 1H), 5.08 (m, 1H), 6.58 (d, 1H), 7.14 (m, 2H), 7.37 (m, 2H), 7.90 (d, 1H), 8.37 (d, 1H)	2,4-dichloro pyrimidine	(2*R*)-2-amino-2-(4-fluoro phenyl)ethanol
3	4-Chloro-*N*-(5-cyclopropyl-1*H*-pyrazol-3-yl)-5-(trifluoromethyl)pyrimidin-2-amine	0.66 (m, 2H), 0.92 (m, 2H), 1.89 (m, 1H), 6.25 (s, 1H), 8.72 (s, 1H), 10.77 (s, 1H), 12.19 (s, 1H)	2,4-dichloro-5-trifluoromethyl pyrimidine	5-cyclopropyl-1*H*-pyrazol-3-amine
4	2-Chloro-4-{[(1*S*)-1-(4-fluorophenyl) ethyl]amino} pyrimidine-5-carbonitrile	MS: Calcd.: 305.1; Found: $[M+H]^+$ 305.2	2,4-dichloro pyrimidine-5-carbonitrile	[(1*S*)-1-(4-fluorophenyl) ethyl]amine
5	(2*R*)-2-[(2-Chloro-5-methylpyrimidin-4-yl)amino]-2-(4-fluorophenyl) ethanol	($CDCl_3$): 2.11 (s, 3H), 4.00 (m, 2H), 5.36 (m, 1H), 5.81 (m, 1H), 7.02 (m, 2H), 7.34 (m, 2H), 7.83 (s, 1H)	2,4-dichloro-5-methylpyrimidine	(2*R*)-2-amino-2-(4-fluoro phenyl)ethanol
6	2-Chloro-*N*-[1-(4-fluorophenyl)ethyl] -5-(trifluoromethyl) pyrimidin-4-amine	Used directly in next step.	2,4-dichloro-5-trifluoromethyl pyrimidine	[1-(4-fluoro phenyl)ethyl] amine

Utility

The compounds of the present invention have utility for the treatment of cancer by inhibiting the tyrosine kinases, particularly the Trks and more particularly Trk A and B. Methods of treatment target tyrosine kinase activity, particularly the Trk activity and more

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

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

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

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

Trk A Assay Format

Trk A kinase activity was measured for its ability to phosphorylate synthetic tyrosine residues within a generic polypeptide substrate using an Amplified Luminescent Proximity Assay (Alphascreen) technology (PerkinElmer, 549 Albany Street, Boston, MA).

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

plates and the reaction products were detected with the addition of strepavidin coated Donor Beads and phosphotyrosine-specific antibodies coated Acceptor Beads using the EnVision Multilabel Plate Reader after an overnight incubation at room temperature.

Peptide substrate	PolyEY-biotin (PGT-bio.)
ATP Km	70 μM
Assay conditions	0.838 ng/ml Trk A, 9 mM HEPES, 45 μg/ml BSA, 10 mM $MnCl_2$, 5 nM PGT-bio, 0.01% Triton® X-100, 70 μM ATP
Incubation	20 minutes, room temperature
Termination/Detection conditions	6.3mM HEPES, 30 mM EDTA, 525 μg/mL BSA, 40 mM NaCl, 0.007%Triton® X-100, 12 ng/ml of Donor Beads, 12 ng/ml of Acceptor Beads
Detection incubation	overnight, room temperature
Fluometer settings	Excitation = 680 nM Emission = 570 nM Excitation Time = 180 ms Total Measurement Time=550 ms

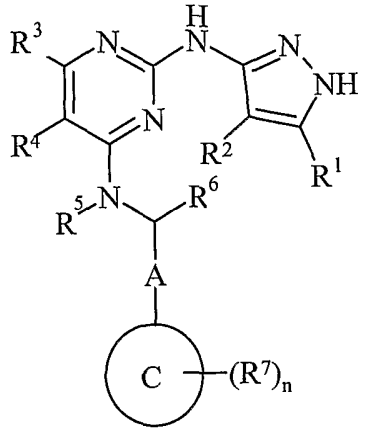
Although the pharmacological properties of the compounds of the formula **(I)** vary with structural change, in general activity possessed by compounds of the formula **(I)** may be demonstrated at IC_{50} concentrations (concentrations to achieve 50% inhibition) or doses in the range of (0.01 μM to 10 μM).

When tested in the above in-vitro assay the Trk inhibitory activity of the following examples was measured at the following IC_{50}s.

Ex	**IC_{50} (μM)**
4	0.036
5	0.106
7	3.94

Claim

1. A compound of formula **(I)**:



(I)

wherein:

R^1 and **R^2** are independently selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R^1 and R^2 independently of each other may be optionally substituted on carbon by one or more R^8; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^3 and **R^4** are independently selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R^3 and R^4 independently of each other may be optionally substituted on carbon by one or more R^{10}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{11};

or **R^3** and **R^4** together with the pyrimidine bond to which they are attached form a 5 or 6 membered carbocyclic ring or a 5 or 6 membered heterocyclic ring wherein said ring is

fused to the pyrimidine of formula **(I)**; wherein the double bonds of the resulting bicyclic ring may be further delocalised across the whole of the bicyclic ring; and wherein said carbocyclic ring or heterocyclic ring may be optionally substituted on carbon by one or more R^{12}; and wherein if said heterocyclic ring contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

R^5 is hydrogen or optionally substituted C_{1-6}alkyl; wherein said optional substituents are selected from one or more R^{14};

R^6 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R^6 may be optionally substituted on carbon by one or more R^{15}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{16};

A is a direct bond or C_{1-2}alkylene; wherein said C_{1-2}alkylene may be optionally substituted by one or more R^{17};

Ring C is carbocyclyl or heterocyclyl;

R^7 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R^7 may be optionally substituted on carbon by one or more R^{18}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{19};

n = 0, 1, 2 or 3; wherein the values of R^7 may be the same or different;

R^8, **R^{10}**, **R^{12}**, **R^{14}**, **R^{15}**, **R^{17}** and **R^{18}** are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl,

N,N-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R^8, R^{10}, R^{12}, R^{14}, R^{15}, R^{17} and R^{18} independently of each other may be optionally substituted on carbon by one or more R^{20}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{21};

R^9, R^{11}, R^{13}, R^{16}, R^{19} and **R^{21}** are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; wherein R^9, R^{11}, R^{13}, R^{16}, R^{19} and R^{21} independently of each other may be optionally substituted on carbon by on or more R^{22};

R^{20} and **R^{22}** are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl or heterocyclyl; wherein R^{20} and R^{22} independently of each other may be optionally substituted on carbon by one or more R^{23}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{24};

R^{23} is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl; and

R^{24} is selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

or a pharmaceutically acceptable salt thereof.

2. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in claim 1 wherein R^1 is selected from C_{1-6}alkyl, C_{1-6}alkoxy or carbocyclyl.

3. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in either claim 1 or claim 2 wherein R^2 is hydrogen.

4. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-3 wherein R^3 is hydrogen.

5. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-4 wherein R^4 is selected from hydrogen, halo, cyano and C_{1-6}alkyl; wherein R^3 and R^4 independently of each other may be optionally substituted on carbon by one or more R^{10}; wherein R^{10} is halo.

6. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-5 wherein R^5 is hydrogen.

7. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-6 wherein R^6 is C_{1-6}alkyl; wherein R^6 may be optionally substituted on carbon by one or more R^{15}; wherein R^{15} is hydroxy.

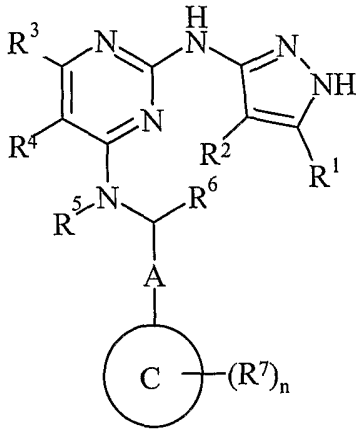
8. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-7 wherein A is a direct bond.

9. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-8 wherein Ring C is carbocyclyl.

10. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-9 wherein R^7 is halo.

11. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-10 wherein n = 0 or 1.

12. A compound of formula **(I)**:



wherein:

R^1 is selected from methyl, methoxy or cyclopropyl;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is selected from hydrogen, chloro, cyano, trifluoromethyl and methyl;

R^5 is hydrogen;

R^6 is methyl or hydroxymethyl;

A is a direct bond;

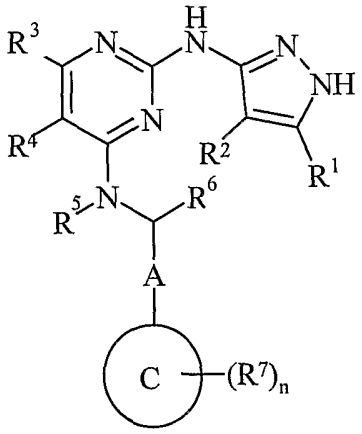
Ring C is phenyl;

R^7 is fluoro;

n = 0 or 1;

or a pharmaceutically acceptable salt thereof.

13. A compound of formula **(I)**:



selected from:

(2R)-2-({5-chloro-2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]pyrimidin-4-yl}amino)-2-(4-fluorophenyl)ethanol;

(2R)-2-({2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]pyrimidin-4-yl}amino)-2-(4-fluorophenyl)ethanol;

(2R)-2-{[2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-5-(trifluoromethyl)pyrimidin-4-yl]amino}-2-(4-fluorophenyl)ethanol;

2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-4-{[(1S)-1-(4-fluorophenyl)ethyl]amino} pyrimidine-5-carbonitrile;

(2R)-2-({2-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-5-methylpyrimidin-4-yl}amino)-2-(4-fluorophenyl)ethanol;

(2R)-2-({5-chloro-2-[(5-isopropoxy-1H-pyrazol-3-yl)amino]pyrimidin-4-yl}amino)-2-(4-fluorophenyl)ethanol;

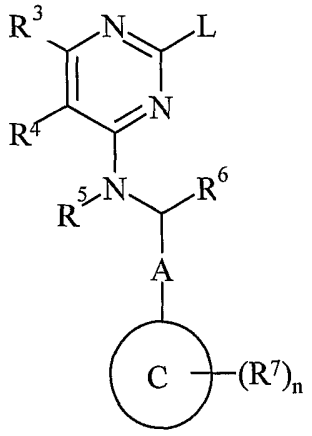
(2R)-2-({5-chloro-2-[(5-methyl-1H-pyrazol-3-yl)amino]pyrimidin-4-yl}amino)-2-(4-fluorophenyl)ethanol;

N^2-(3-cyclopropyl-1H-pyrazol-5-yl)-N^4-(1-phenylethyl)-5-(trifluoromethyl)pyrimidine-2,4-diamine;

or a pharmaceutically acceptable salt thereof.

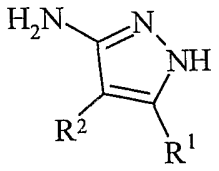
14. A process for preparing a compound of formula **(I)** or a pharmaceutically acceptable salt thereof which process, wherein variable groups are, unless otherwise specified, as defined in claim 1, comprises of:

Process a) reaction of a pyrimidine of formula **(II)**:



(II)

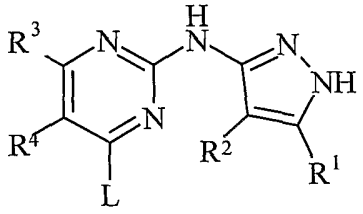
wherein L is a displaceable group; with an pyrazole amine of formula **(III)**:



(III)

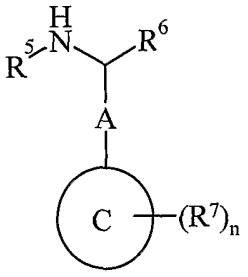
or

Process b) reacting a pyrimidine of formula **(IV)**:



(IV)

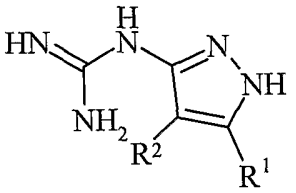
wherein L is a displaceable group; with a compound of formula **(V)**:



(V)

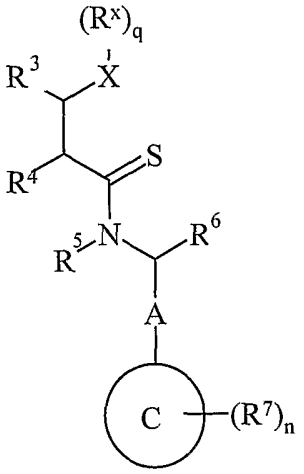
or

Process c) reacting a compound of formula **(VI)**:



(VI)

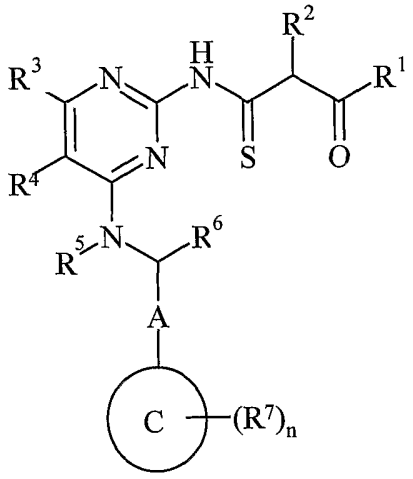
with a compound of formula **(VII)**:



(VII)

wherein X is an oxygen atom and q is 1; or X is a nitrogen atom and q is 2; and wherein each R^x independently represents a C_{1-6}alkyl group; or

Process d) reacting a compound of formula **(VIII)**:



(VIII)

with hydrazine;

and thereafter if necessary:

i) converting a compound of the formula **(I)** into another compound of the formula **(I)**;

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt.

15. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-13, for use as a medicament.

16. The use of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-13, in the manufacture of a medicament for use in the inhibition of Trk activity.

17. The use of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-13, in the manufacture of a medicament for use in the treatment or prophylaxis of cancer.

18. The use of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-13, in the manufacture of a medicament for use in the production of an anti-proliferative effect.

19. A method of inhibiting Trk activity comprising administering to a host in need of such treatment a therapeutically effective amount of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-13.

20. A method for the treatment or prophylaxis of cancer comprising administering a therapeutically effective amount of a compound of formula **(I)** or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-13.

21. A method of producing an anti-proliferative effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-13.

22. A pharmaceutical composition comprising a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-13, together with at least one pharmaceutically acceptable carrier, diluent or excipient.

23. A pharmaceutical composition comprising a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-13, together with at least one pharmaceutically acceptable carrier, diluent or excipient for use in the inhibition of Trk activity.

24. A pharmaceutical composition comprising a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-13, together with at least one pharmaceutically acceptable carrier, diluent or excipient for use in the treatment or prophylaxis of cancer.

25. A pharmaceutical composition comprising a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-13, together with at least one pharmaceutically acceptable carrier, diluent or excipient for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

26. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-13, for use in the inhibition of Trk activity.

27. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-13, for use in the treatment or prophylaxis of cancer.

28. A compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1-13, for use in the production of an anti-proliferative effect.

29. The method or use according to claims 17, 20, 24 or 27 wherein said cancer is selected from congenital fibrosarcoma, mesoblastic nephroma, mesothelioma, acute myeloblastic leukemia, acute lymphocytic leukemia, multiple myeloma, melanoma, oesophageal cancer, myeloma, hepatocellular, pancreatic, cervical cancer, Ewings sarcoma, neuroblastoma, Kaposi sarcoma, ovarian cancer, breast cancer including secretory breast cancer, colorectal cancer, prostate cancer including hormone refractory prostate cancer, bladder cancer, melanoma, lung cancer - non small cell lung cancer (NSCLC), and small cell lung cancer (SCLC), gastric cancer, head and neck cancer, renal cancer, lymphoma, thyroid cancer including papillary thyroid cancer, mesothelioma and leukaemia.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/001622

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/12 A61K31/505 A61P35/00

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/056786 A (PFIZER PRODUCTS INC; KATH, JOHN, CHARLES; LUZZIO, MICHAEL, JOSEPH) 8 July 2004 (2004-07-08) Examples pages 1,2; claims 1,13,14	1-29
Y	EP 1 345 925 A (VERTEX PHARMACEUTICALS INCORPORATED) 24 September 2003 (2003-09-24) cited in the application Table 3, compounds IIc-3, IIc-5, IIc-10, IIc-13, IIc-28, IIc-29, IIc-35, IIc-38, IIc-47, IIc-69 general formulas IId on page 33 and IIIc on page 36 Biological tests on pages 58-60 Schemes I-V page 2, paragraph 1-5; claim 1	1-29

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 July 2006	31/07/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Guspanova, J

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/030909 A (BAYER CORPORATION; NAGARATHNAM, DHANAPALAN; WANG, CHUNGUANG; CHEN, YUA) 17 April 2003 (2003-04-17) pages 1,90,91; claims 1,9,10,12,14	1-29
Y	EP 1 317 447 A (VERTEX PHARMACEUTICALS INCORPORATED) 11 June 2003 (2003-06-11) page 1, paragraph 1-5 page 7, paragraph 33-35 compounds 1 and 2 on page 11 compound VII on page 31 Biological tests on pages 58 and 59 page 8, paragraphs 41,47; claims 1,39,40,52-54	1-29
Y	WO 03/026664 A (BAYER CORPORATION; DIXON, JULIE; DUMAS, JACQUES; BRENNAN, CATHERINE; H) 3 April 2003 (2003-04-03) page 1, paragraphs 1,2 page 2, line 26 - page 3, line 7 page 3, line 28 - page 4, line 13 page 24, line 11 - page 28, line 11; claims 1,21,25-27	1-29
Y,P	WO 2005/103010 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; LYNE, PAUL; WANG, BIN; WANG, T) 3 November 2005 (2005-11-03) cited in the application page 1, lines 4-13 biological tests on pages 43-45 page 2, line 20 - page 3, line 13; claims 1,12-19	1-29
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2006/001622

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

Although claims 19-21 and 29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2006/001622

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Information on patent family members

International application No
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