Title: PYRIMIDINE COMPOUNDS HAVING A FGFR INHIBITORY EFFECT

Abstract: There is provided pyrimidine compounds of formula (I): or pharmaceutical salts thereof. There is also provided processes for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy, for example in the treatment of proliferative disease such as cancer and particularly in disease mediated by a FGFR inhibitory effect.
The present invention relates to pyrimidine compounds, a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

Protein kinases are a class of proteins (enzymes) that regulate a variety of cellular functions. This is accomplished by the phosphorylation of specific amino acids on protein substrates resulting in conformational alteration of the substrate protein. The conformational change modulates the activity of the substrate or its ability to interact with other binding partners. The enzyme activity of the protein kinase refers to the rate at which the kinase adds phosphate groups to a substrate. It can be measured, for example, by determining the amount of a substrate that is converted to a product as a function of time. Phosphorylation of a substrate occurs at the active-site of a protein kinase.

Tyrosine kinases are a subset of protein kinases that catalyze the transfer of the terminal phosphate of adenosine triphosphate (ATP) to tyrosine residues on protein substrates. These kinases play an important part in the propagation of growth factor signal transduction that leads to cellular proliferation, differentiation and migration.

Fibroblast growth factor (FGF) has been recognized as an important mediator of many physiological processes, such as morphogenesis during development and angiogenesis. There are currently over 25 known members of the FGF family. The fibroblast growth factor receptor (FGFR) family consists of four members with each composed of an extracellular ligand binding domain, a single transmembrane domain and an intracellular cytoplasmic protein tyrosine kinase domain. Upon stimulation with FGF, FGFRs undergo dimerisation and transphosphorylation, which results in receptor activation. Receptor activation is sufficient for the recruitment and activation of specific downstream signalling partners that participate in the regulation of diverse process such as cell growth, cell metabolism and cell survival (Reviewed in Eswarakumar, V.P. et. al., Cytokine & Growth Factor Reviews 2005, 16, pl39-149). Consequently, FGF and FGFRs have the potential to initiate and/or promote tumorigenesis.

There is now considerable evidence directly linking FGF signalling to human cancer. The elevated expression of various FGFs has been reported in a diverse range of tumour types such as bladder, renal cell and prostate (amongst others). FGF has also been described as a powerful angiogenic factor. The expression of FGFRs in endothelial cells has also been
reported. Activating mutations of various FGFRs have been associated with bladder cancer and multiple myeloma (amongst others) whilst receptor expression has also been documented in prostate and bladder cancer amongst others (Reviewed in Grose, R. et al., Cytokine & Growth Factor Reviews 2005, 16, p179-186 and Kwabi-Addo, B. et al., Endocrine-Related Cancer 2004, 11, p709-724). For these reasons, the FGF signalling system is an attractive therapeutic target, particularly since therapies targeting FGFRs and/or FGF signalling may affect both the tumour cells directly and tumour angiogenesis.

In accordance with the present invention, there is provided a compound of formula (I):

\[
\begin{align*}
\text{(I)} & \\
R^1 & \text{represents a Ci-C}_6\text{alkyl optionally substituted by one or more } R^{13}, \\
R^2 & \text{hydrogen or } \\
\end{align*}
\]

wherein

- \( R^1 \) represents a Ci-C\(_6\)alkyl optionally substituted by one or more \( R^{13} \),
- a C\(_3\)-C\(_5\)cycloalkyl optionally substituted by one or more \( R^{14} \),
- a C\(_2\)-C\(_6\)alkenyl optionally substituted by one or more \( R^{15} \),
- a 4- to 6-membered heterocyclyl group optionally substituted by one or more \( R^{16} \),
- a Ci-C\(_6\)alkoxy group optionally substituted by one or more \( R^{17} \),
- a C3-Ci2carbocyclyloxy group optionally substituted by one or more \( R^{18} \),
- a 5- to 6-membered heterocyclyloxy group optionally substituted by one or more \( R^{19} \),
- a \(-S(O)_xR^5\) group,
- a \(-S(O)_2NR^6R^7\) group, or
- \(-A-B;\)

\( R^2 \) represents hydrogen or
a Ci-C₃alkyl group optionally substituted by one or more substituents selected from Ci-C₃alkoxy, cyano, hydroxyl, amino (-NH₂), mono-Ci-C₃alkyamino and di-(Ci-C₃alky)amino;

R⁴ represents hydrogen,

5 a Ci-C₆alkyl group optionally substituted with Ci-C₃alkoxy, hydroxyl, amino (-NH₂), mono-Ci-C₃alkyamino and di-(Ci-C₃alky)amino,

a Ci-C₆alkenyl group optionally substituted with Ci-C₃alkoxy,

a Ci-C₆alkynyl group optionally substituted with Ci-C₃alkoxy,

a C₃-C₅cycloalkyl group optionally substituted with Ci-C₃alkoxy,

a Ci-C₃alkoxy group optionally substituted with Ci-C₃alkoxy, hydroxyl, amino (-NH₂), mono-Ci-C₃alkyamino and di-(Ci-C₃alky)amino,

-C(O)NR⁸R⁹,

-NR¹⁰R¹¹,

-S(O)₂R¹²;

A represents a C₂-alkylene optionally substituted by one or more R²⁰,
a Ci-alkyleneoxy optionally substituted by one or more R²¹, or
an oxyCi-alkylene optionally substituted by one or more R²²;

B represents a 5- or 6-membered aromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the aromatic ring being optionally substituted by one or more R²³ and optionally wherein two or more adjacent R²³ together with the atoms to which they are attached form a partially or fully unsaturated 4- to 6-membered ring;

25 R⁵ represents a Ci-C₆alkyl, C₅-Cycloalkyl or -CH₂Ar wherein Ar represents a 5- or 6-membered aromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the aromatic ring being optionally substituted by one or more R²⁴ and optionally wherein two or more adjacent R²⁴ together with the atoms to which they are attached form a partially or fully unsaturated 4- to 6-membered ring;
R\textsuperscript{6} and R\textsuperscript{7} each independently represent hydrogen, \(\text{Ci-C}_4\)alkyl or \(\text{C}_3\)Cecycloalkyl, or R\textsuperscript{6} and R\textsuperscript{7} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle optionally comprising an additional heteratom selected from oxygen, sulphur or nitrogen wherein each R\textsuperscript{6} and R\textsuperscript{7} independently may be optionally substituted on carbon by one or more substituents R\textsuperscript{25} and wherein if said heterocycle contains an \(-\text{NH}-\) moiety that nitrogen may be optionally substited by a group selected from R\textsuperscript{26} ;

R\textsuperscript{8} and R\textsuperscript{9} each independently represent hydrogen, \(\text{Ci-C}_4\)alkyl or \(\text{C}_3\)Cecycloalkyl, or R\textsuperscript{8} and R\textsuperscript{9} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle optionally comprising an additional heteratom selected from oxygen, sulphur or nitrogen wherein each R\textsuperscript{8} and R\textsuperscript{9} independently may be optionally substituted on carbon by one or more substituents R\textsuperscript{27} and wherein if said heterocycle contains an \(-\text{NH}-\) moiety that nitrogen may be optionally substited by a group selected from R\textsuperscript{28} ;

R\textsuperscript{10} and R\textsuperscript{11} each independently represent hydrogen, \(\text{Ci-C}_4\)alkyl or \(\text{C}_3\)Cecycloalkyl, or R\textsuperscript{10} and R\textsuperscript{11} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle optionally comprising an additional heteratom selected from oxygen, sulphur or nitrogen wherein each R\textsuperscript{10} and R\textsuperscript{11} independently may be optionally substituted on carbon by one or more substituents R\textsuperscript{29} and wherein if said heterocycle contains an \(-\text{NH}-\) moiety that nitrogen may be optionally substited by a group selected from R\textsuperscript{30} ;

R\textsuperscript{12} represents \(\text{Ci-C}_6\)alkyl or \(\text{C}_3\)Cecycloalkyl;

R\textsuperscript{13}, R\textsuperscript{14}, R\textsuperscript{15}, R\textsuperscript{20}, R\textsuperscript{21}, R\textsuperscript{22}, R\textsuperscript{36} and R\textsuperscript{38} each independently is \(-\text{NR}^3\text{R}^3\), \(-\text{C(O)}\text{NR}^3\text{R}^3\) cyano, hydroxyl or a group selected from d-\(\text{C}_6^3\)alkyl, d-\(\text{C}_6^3\)alkoxy, C3-C6cycloalkyl, \(\text{Ci-C}_6^3\)alkylthio wherein said group may be optionally substited by one or more R\textsuperscript{31} ;

R\textsuperscript{16} and R\textsuperscript{17} each independently is selected from R\textsuperscript{36} and a 5- or 6-membered aromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, wherein the aromatic ring is optionally substited by one or more substituents selected from R\textsuperscript{37} ;

R\textsuperscript{18}, R\textsuperscript{19}, R\textsuperscript{37} and R\textsuperscript{42} each independently is R\textsuperscript{38}, \(-\text{SO}_2\text{NR}^3\text{R}^3\) nitro, carboxyl or a group selected from a C\textsubscript{2}Cealkenyl, \(\text{Ci-C}_6^3\)alkoxycarbonyl, \(\text{Ci-C}_6^3\)alkylcarbonyl,
Ci-Cealkylcarbonylamino, phenylcarbonyl, -S(O)\textsubscript{m} Ci-C\textsubscript{6}alkyl wherein said group may be optionally substituted by one or more R\textsuperscript{41};

R\textsuperscript{23} and R\textsuperscript{24} each independently is R\textsuperscript{42}, -OS(O)\textsubscript{2} Ci-C\textsubscript{6}alkyl or a group selected from phenyl, benzyl, benzyloxy wherein said group may be optionally substituted by one or more R\textsuperscript{43};

R\textsuperscript{25}, R\textsuperscript{27}, R\textsuperscript{29}, R\textsuperscript{31}, R\textsuperscript{41}, R\textsuperscript{43}, R\textsuperscript{44}, R\textsuperscript{46} and R\textsuperscript{48} each independently is selected from halogen, Ci-C\textsubscript{6}alkyl, Ci-C\textsubscript{6}alkoxy, Ci-C\textsubscript{6}alkylthio, amino (-NH\textsubscript{2}), mono- and di-

Ci-Cealkyamino, cyano, hydroxyl and trifluoromethyl;

R\textsuperscript{26}, R\textsuperscript{28}, R\textsuperscript{30}, R\textsuperscript{45}, R\textsuperscript{47} and R\textsuperscript{49} each independently is selected from Ci-C\textsubscript{6}alkyl, benzyl, Ci-C\textsubscript{6}alkoxycarbonyl, Ci-C\textsubscript{6}alkylcarbonyl, phenylcarbonyl, Ci-C\textsubscript{6}alkylsulphonyl and phenylsulphonyl;

R\textsuperscript{32} and R\textsuperscript{33} each independently represent hydrogen, Ci-C\textsubscript{4}alkyl or C\textsubscript{3}-Cecycloalkyl, or

R\textsuperscript{32} and R\textsuperscript{33} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle optionally comprising an additional heteratom selected from oxygen, sulphur or nitrogen wherein each R\textsuperscript{32} and R\textsuperscript{33} independently may be optionally substituted on carbon by one or more substituents R\textsuperscript{44} and wherein if said heterocycle contains an -NH- moiety that nitrogen may be optionally substited by a group selected from R\textsuperscript{45};

R\textsuperscript{34} and R\textsuperscript{35} each independently represent hydrogen, Ci-C\textsubscript{4}alkyl or C\textsubscript{3}-Cecycloalkyl, or

R\textsuperscript{34} and R\textsuperscript{35} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle optionally comprising an additional heteratom selected from oxygen, sulphur or nitrogen wherein each R\textsuperscript{34} and R\textsuperscript{35} independently may be optionally substituted on carbon by one or more R\textsuperscript{46} and wherein if said heterocycle contains an -NH- moiety that nitrogen may be optionally substited by a group selected from R\textsuperscript{47};

R\textsuperscript{39} and R\textsuperscript{40} each independently represent hydrogen, Ci-C\textsubscript{4}alkyl or C\textsubscript{3}-Cecycloalkyl, or

R\textsuperscript{39} and R\textsuperscript{40} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle optionally comprising an additional heteratom selected from oxygen, sulphur or nitrogen wherein each R\textsuperscript{39} and R\textsuperscript{40} independently may be optionally substituted on carbon by one or more R\textsuperscript{48} and wherein if said heterocycle contains an -NH- moiety that nitrogen may be optionally substited by a group selected from R\textsuperscript{49};
m is 0, 1 or 2;
x is 0, 1 or 2;
y is 0, 1 or 2; and

wherein

(i) when \( R^1 \) is an optionally substituted \( C_2^-C_6 \)alkenyl, 4- to 6-membered heterocyclyl group, \( C_3^-C_6 \)alkoxy group, \( C_1^-C_2 \)carbocyclyloxy, 5- to 6-membered heterocyclyloxy, \(-S(O)_xR^5\), \(-S(O)_2NR^6R^7\) or \(-A-B\) group,

\[ R^3 \] represents a \( C_i^-C_5 \)alkyl group optionally substituted by one or more substituents selected from \( d-C_3^-C_6 \)alkoxy, cyano, hydroxyl, amino \((-NH_2)\), mono-\( C_3^-C_6 \)alkylamino and di-(\( C_3^-C_6 \)alkyl)amino,
a \( C_3^-C_5 \)cycloalkyl group optionally substituted by one or more substituents selected from \( C_3^-C_6 \)alkyl and \( C_3^-C_6 \)alkoxy,
a 3- to 5-membered saturated heterocyclyl group optionally substituted with by one or more substituents selected from \( C_3^-C_6 \)alkyl,

\( C_i^-C_6 \)alkoxy and \( C_3^-C_6 \)cycloalkyl,
a 5- or 6-membered aromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur,
a mono-\( C_i^-C_3 \)alkylaminocarbonyl group,
a di-(\( C_i^-C_3 \)alkyl)aminocarbonyl group,
a \( C_i^-C_6 \)alkoxy carbonyl group,
a \(-CONH_2\) group,
a \(-CO_2H\) group;

or (ii) when \( R^1 \) is an optionally substituted \( C_i^-C_6 \)alkyl or a \( C_3^-C_5 \)cycloalkyl group,

\[ R^3 \] represents a \( d-C_6 \)alkyl group optionally substituted by one or more substituents selected from \( C_i^-C_3 \)alkoxy, cyano, hydroxyl, amino \((-NH_2)\), mono-\( C_i^-C_3 \)alkylamino and di-(\( C_i^-C_3 \)alkyl)amino,
a \( C_3^-C_6 \)cycloalkyl group optionally substituted with \( C_i^-C_3 \)alkoxy,
a 3- to 5-membered saturated heterocyclyl group optionally substituted with by one or more substituents selected from \( C_i^-C_3 \)alkyl,

\( C_i^-C_6 \)alkoxy and \( C_3^-C_5 \)cycloalkyl,
a \(-CONH_2\) group,
a \(-CO_2H\) group;
or a pharmaceutically acceptable salt thereof.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups. References to individual straight chain alkyl groups such as "n-propyl" are specific for the straight chain version only and references to individual branched chain alkyl groups such as "isopropyl" or "/propyl" are specific for the branched chain version only. Examples of "Ci-C6alkyl" include methyl, ethyl, n-propyl, /-propyl, butyl, /-butyl, t-butyl, n-pentyl, /-pentyl, neopentyl and hexyl. Examples of "C1-C4alkyl" include methyl, ethyl, n-propyl, /-propyl, n-butyl, /-butyl and t-butyl. A similar convention applies to other radicals, for example, examples of "Ci.Cealkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, n-propoxy carbonyl, /-propoxy carbonyl, butoxy carbonyl, /-butoxy carbonyl, n-pentoxy carbonyl, /-pentoxy carbonyl, neopentoxy carbonyl and hexoxy carbonyl. Examples of "Ci.C6alkylthio" include methylthio, ethylthio, n-propylthio, /-propylthio, n-butythio, /-butythio, pentylthio, /-pentylthio, neopentylthio and hexylthio. Examples of "Ci.Cealkylcarbonylamino" include formamido, acetamido and propionylamino. Examples of "S(O)mCi.C6alkyl", "SCCOxCi.Cealkyl" and "S(O)yCi.C6alkyl" wherein m is 0, 1 or 2 include Ci-Cealkylthio, Ci-C6alkylsulphinyl and Ci-C6alkylsulphonyl, for example methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "Ci.Cealkylcarbonyl" include methylcarbonyl (acetyl), ethylcarbonyl (propionyl), propylcarbonyl, /-propylcarbonyl, butylcarbonyl, /-butylcarbonyl, t-butylcarbonyl, pentylcarbonyl, /-pentylcarbonyl, neopentylcarbonyl and hexylcarbonyl. Examples of "C2-C6alkenyl" include vinyl, allyl, 1-propenyl, butenyl and isobutenyl. Examples of "Ci.C6alkynyl" include acetylenyl and propargyl. Examples of "mono- and di-Ci.Cealkylamino" include methylamino, ethylamino, n-propylamino, /-propylamino, n-butylamino, /-butylamino, t-butylamino, n-pentylamino, /-pentylamino, neopentylamino, hexamino, dimethylamino, diethylamino and ethylmethylamino.

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.

The term "halo" refers to fluoro, chloro, bromo and iodo.
The term "amino" refers to a -NH₂ group.

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 -CH₂- 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, pyrazolyl, isothiazolyl, indolyl, quinolyl, thienny, 1,3-benzodioxolyl, thiadiazolyl, piperazinyl, thiazolidinyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, tetrahydropyranyl, imidazolyl, pyrimidyl, pyrazinyl, isoxazolyl, 7H-methylpyrrolyl, 4-pyridone, 1-isoquinolone, 2-pyrrolidone, 4-thiazolidone, pyridine-7H-oxide and quinoline-7H-oxide.

In one aspect of the invention a "4- to 6-membered heterocyclic group", is a saturated, partially saturated or unsaturated, monocyclic ring containing 4, 5 or 6 atoms of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur, it may, unless otherwise specified, be carbon or nitrogen linked, a -CH₂- group can optionally be replaced by a -C(O)- and a ring sulphur atom may be optionally oxidised to form the S-oxides. Suitable "4- to 6-membered heterocyclic group" which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur" include tetrahydrofuran, tetrahydrofuranone, 2-methoxybutyrolactone, alpha-pyran, gamma-pyran, dioxolane, tetrahydropyran, dioxane, dihydrothiophene, thiolan, dithiolan, pyrroline, pyrrolidine, pyrazoline, pyrazolidine, imidazoline, imidazolidine, tetrazole, piperidine, pyridazine, pyrimidine, pyrazine, piperazine, triazine, tetrazine, morpholine, thiomorpholine, thiomorpholine S,S-dioxide, diazepan, oxazine, tetrahydro-oxazinyl, isothiazole, oxetane, azetidine, and pyrazolidine.

In one aspect of the invention a "5- or 6-membered aromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur" is a fully unsaturated, aromatic monocyclic ring containing 5 or 6 atoms of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur, which may, unless otherwise specified, be carbon or nitrogen linked. Suitable "5- or 6-membered aromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur" include furyl, imidazolyl, isothiazolyl, isoxazolyl, oxazolyl, phenyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, thiazolyl, thienyl and triazolyl rings.

A "carbocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic
carbon ring that contains 3-12 atoms; wherein a -CH₂- group can optionally be replaced by a -C(O)-. Particularly "carbocyclyl" is a monocyclic ring containing 3 to 6 atoms or a bicyclic ring containing 9 or 10 atoms. Examples of "carbocyclyl" include cycloalkyl and aryl rings. Suitable values for "carbocyclyl" include cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl, naphthyl, tetralinyl, indanyl or 1-oxoindanyl.

In one aspect of the invention a "C₃₋₆ Cycloalkyl" is a saturated monocyclic ring containing 3 or 6 atoms. Examples of "C₃₋₆ cycloalkyl" include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

A "C₃-Ci₂carbocyclyloxy group" and "5- to 6-membered heterocyclyloxy" denotes an -OR group wherein R is either a 3- to 10-membered carbocyclyl group or a 5- to 6-membered heterocyclyl group as defined above.

A "C₅arylxy group" and "5- to 6-membered heteroaryloxy" denotes an -OR group wherein R is a 6-membered aromatic ring, for example phenyl, or a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur for example furyl, imidazolyl, isothiazolyl, isoxazolyl, oxazolyl, phenyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, thiazolyl, thi enyl or triazolyl.

A "C₂-alkylene" denotes a two carbon saturated linking group. For example, an unsubstituted C₂-alkylene group is a -CH₂CH₂- linking group.

A "C₁-alkyleneoxy" denotes a two atom saturated linking group comprising one carbon and one oxygen atom. For example, an unsubstituted Q-alkyleneoxy group is a -CH₂O- linking group (and for example the group -A-B is -CH₂O-B).

An "oxyC₁-alkylene" denotes a two atom saturated linking group comprising one carbon and one oxygen atom. For example, an unsubstituted Ci-alkyleneoxy group is a -OCH₂- linking group (and for example the group -A-B is -OCH₂-B).

When B represents a 5- or 6-membered aromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring being optionally substituted by at least two adjacent substituents and wherein the two or more adjacent substituents together with the atoms to which they are attached form a partially or fully unsaturated 4- to 6-membered ring, examples of B include indole, indoline, benzo thiophen, benzofuran, benzimidazole and benzodioxole.
When $R^3$ represents a 3- to 5-membered saturated heterocyclyl group, examples of the 3- to 5-membered saturated heterocyclyl group include oxirane, aziridine, azetidine and pyrrolidine.

When $R^6$ and $R^7$, or $R^8$ and $R^9$, or $R^{10}$ and $R^{11}$, or $R^{32}$ and $R^{33}$, or $R^{34}$ and $R^{35}$, or $R^{39}$ and $R^{40}$ represent a saturated heterocycle, it should be understood that when the heterocycle comprises only one heteroatom, the heteroatom present is the nitrogen atom to which $R^6$ and $R^7$, or $R^8$ and $R^9$, or $R^{10}$ and $R^{11}$, or $R^{32}$ and $R^{33}$, or $R^{34}$ and $R^{35}$, or $R^{39}$ and $R^{40}$ are attached. Examples of 4- to 6-membered saturated heterocycles include pyrrolidinyl, piperidinyl and morpholinyl.

Particular values of variable groups are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In one embodiment of the invention, $R^1$ represents

- a $C_i-C_6$alkoxy group optionally substituted by one or more $R^{17}$;
- a $C_3-Ci2$carbocyclyloxy group optionally substituted by one or more $R^{18}$; or
- a 5- to 6-membered heterocyclyloxy group optionally substituted by one or more $R^{19}$.

In another embodiment of the invention, $R^1$ represents

- a $C_i-C_6$alkoxy group optionally substituted by one or more $R^{17}$;
- a $C_6$aryloxy group optionally substituted by one or more $R^{18}$; or
- a 5- to 6-membered heteroaryloxy group optionally substituted by one or more $R^{19}$.

In another embodiment of the invention, $R^1$ represents

- a $C_i-C_6$alkoxy group.
- a $C_3-C_5$alkoxy group.
- a $z$-propoxy group.
In another embodiment of the invention, \( R^1 \) represents a \( Ci-C_6 \)alkyl optionally substituted by one or more \( R^{13} \).

In a further embodiment of the invention, \( R^1 \) represents a \( Ci-C_6 \)alkyl group substituted by one or more substituents selected from \( Ci-C_6 \)alkoxy (which may be optionally substituted by one or more substituents selected from halogen, \( d-C_6 \)alkyl, \( Ci-C_6 \)alkoxy, \( Ci-C_6 \)alkylthio, amino (-NH\(_2\)), mono- and di-\( Ci-C_6 \)alkylamino, cyano, hydroxyl and trifluoromethyl) and hydroxyl.

In a further embodiment of the invention \( R^1 \) represents a \( C_3-C_6 \)cycloalkyl optionally substituted by one or more \( R^{14} \).

In one embodiment of the invention \( R^1 \) represents a 4- to 6-membered heterocyclyl group optionally substituted by one or more \( R^{16} \).

In one embodiment of the invention \( R^1 \) represents -A-B wherein

A represents a C2-alkylene optionally substituted by one or more \( R^{20} \),

a \( Ci \)-alkyleneoxy optionally substituted by one or more \( R^{21} \), or

a oxy\( Ci \)-alkylene optionally substituted by one or more \( R^{22} \); and

B represents a 5- or 6-membered aromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the aromatic ring being optionally substituted by one or more \( R^{23} \) and optionally wherein two or more adjacent \( R^{23} \) together with the atoms to which they are attached form a partially or fully unsaturated 4- to 6-membered ring.

In another embodiment of the invention \( R^1 \) represents -A-B wherein

A represents a C2-alkylene optionally substituted by one or more \( R^{20} \), or

a oxy\( Ci \)-alkylene optionally substituted by one or more \( R^{22} \); and

B represents a 5- or 6-membered aromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the aromatic ring being optionally substituted by one or more \( R^{23} \) and optionally wherein two or more adjacent \( R^{23} \) together with the atoms to which they are attached form a partially or fully unsaturated 4- to 6-membered ring.

In a further embodiment of the invention \( R^1 \) represents -A-B wherein

A represents a C2-alkylene optionally substituted by one or more \( R^{20} \), or
a oxyCi-alkylene optionally substituted by one or more R^22; and
B represents a phenyl ring or a pyridin-4-yl ring each optionally substituted by one or more R^23 and optionally wherein two or more adjacent R^23 together with the atoms to which they are attached form a partially or fully unsaturated 4- to 6-membered ring.

In a further embodiment of the invention R^1 represents -A-B wherein
A represents a C2-alkylene optionally substituted by one or more R^20, or a oxyCi-alkylene optionally substituted by one or more R^22; and
B represents a phenyl ring optionally substituted by one or more R^23 and optionally wherein two or more adjacent R^23 together with the atoms to which they are attached form a partially or fully unsaturated 4- to 6-membered ring.

In a further embodiment of the invention R^1 represents -A-B wherein
A represents a C2-alkylene optionally substituted by one or more R^20; and
B represents a phenyl ring or a pyridin-4-yl ring each optionally substituted by one or more R^23 and optionally wherein two or more adjacent R^23 together with the atoms to which they are attached form a partially or fully unsaturated 4- to 6-membered ring.

In a further embodiment of the invention R^1 represents -A-B wherein
A represents an oxyCi-alkylene optionally substituted by one or more R^22; and
B represents a phenyl ring or a pyridin-4-yl ring each optionally substituted by one or more R^23 and optionally wherein two or more adjacent R^23 together with the atoms to which they are attached form a partially or fully unsaturated 4- to 6-membered ring.

In a further embodiment of the invention R^1 represents -A-B wherein
A represents a -CH_2CH_2- or a -OCH_2-; and
B represents a phenyl ring or a pyridin-4-yl ring each optionally substituted by one or more R^23 and optionally wherein two or more adjacent R^23 together with the atoms to which they are attached form a partially or fully unsaturated 4- to 6-membered ring.

In a further embodiment of the invention R^1 represents -A-B wherein
A represents a -CH_2CH_2- or a -OCH_2-; and
B represents a phenyl ring optionally substituted by one or more substituents selected from d-C₆ alkyl, d-C₆ alkoxy, Ci-C₆ alkoxy carbonyl, Ci-C₆ alkyl carbonylamino, phenyl, -NR₃²R₃³, -C(O)NR₃⁴R₃⁵, (each of which may be optionally substituted by one or more substituents selected from halogen, Ci-C₆ alkyl, Ci-C₆ alkoxy, amino (-NH₂), mono- and di-Ci-C₆ alkylamino, hydroxyl and trifluoromethyl), halogen, nitro, cyano, carboxyl and hydroxyl, and optionally wherein two or more adjacent substituents together with the atoms to which they are attached form a partially or fully unsaturated 4- to 6-membered ring.

In a further embodiment of the invention R¹ represents -A-B wherein

A represents a -CH₂CH₂⁻ or a -OCH₂⁻; and

B represents a phenyl ring or a pyridin-4-yl ring each optionally substituted by one or more substituents selected from Ci-C₆ alkyl, Ci-C₆ alkoxy, Ci-C₆ alkoxy carbonyl, Ci-C₆ alkyl carbonylamino, phenyl, -NR₃²R₃³, -C(O)NR₃⁴R₃⁵, (each of which may be optionally substituted by one or more substituents selected from halogen, d-C₆ alkyl, d-C₆ alkoxy, amino (-NH₂), mono- and di-Ci-C₆ alkylamino, hydroxyl and trifluoromethyl), halogen, cyano, carboxyl and hydroxyl, and optionally wherein two or more adjacent substituents together with the atoms to which they are attached form a partially or fully unsaturated 4- to 6-membered ring; and wherein

R₃² and R₃³ each independently represent hydrogen, C₁-C₄, particularly Ci-C₂ alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyli) or C₃-Cecycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), or R⁶¹ and R⁶² together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (such as pyrrolidinyl, morpholinyl or piperidinyl); and

R₃⁴ and R₃⁵ each independently represent hydrogen, C₁-C₄, particularly Ci-C₂ alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyli) or C₃-Cecycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), or R₆³ and R₆⁴ together with the nitrogen atom to
which they are attached form a 4- to 6-membered saturated heterocycle
(such as pyrrolidinyl, morpholiny or piperidinyl).

In a further embodiment of the invention R1 represents -A-B wherein
A represents -CH2CH2- or -OCH2-; and
B represents a phenyl ring or a pyridin-4-yl ring each optionally substituted by one
or more substituents selected from d-C6alkyl, Ci-C6alkoxy,
Ci-C6alkoxycarbonyl, Ci-Coalkycarbonylamino, phenyl, -NR32R33,
-C(O)NR34R35, (each of which may be optionally substituted by one or
more substituents selected from halogen, Ci-C6alkyl, Ci-C6alkoxy,
amino (-NH2), mono- and di-Ci-C6alkylamino, hydroxyl and
trifluoromethyl), halogen, cyano, carboxyl and hydroxyl; and wherein
R32 and R33 each independently represent hydrogen, C1-C4, particularly Ci-C2alkyl
(such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or
tert-butyl) or C3-Cecycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl
and cyclohexyl), or R61 and R62 together with the nitrogen atom to
which they are attached form a 4- to 6-membered saturated heterocycle
(such as pyrrolidinyl, morpholiny or piperidinyl); and

R34 and R35 each independently represent hydrogen, Ci-C4, particularly Ci-C2alkyl
(such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or
tert-butyl) or C3-Cecycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl
and cyclohexyl), or R63 and R64 together with the nitrogen atom to
which they are attached form a 4- to 6-membered saturated heterocycle
(such as pyrrolidinyl, morpholiny or piperidinyl).

In another embodiment of the invention R1 represents
a Ci-C3alkyl group substituted by one or more substituents selected from
hydroxyl and Ci-C3alkoxy which may be optionally substituted by one or more
substituents selected from halogen, Ci-C3alkyl and Ci-C3alkoxy,
a Ci-C3alkoxy group optionally substituted by one or more substituents
selected from Ci-C3alkoxy and cyclopropyl,
a phenoxy group optionally substituted by one or more substituents selected
from Ci-C3alkyl, Ci-C3alkoxy and cyclopropyl, or
-A-B wherein A represents a C2-alkylene or oxyC2-alkylene, and B represents a phenyl or pyridin-4yl ring wherein the phenyl or the pyridin-4yl ring may be optionally substituted by one or more R23.

In a further additional aspect of the invention R1 represents a hydroxymethyl, methoxypropyl, ethoxypropyl, phenylethyl, 2-(3-methoxyphenyl)ethyl, 2-(3,5-dimethoxyphenyl)ethyl, 2-propoxy, benzyloxy, (3,5-dimethoxyphenyl)methoxy, 2-(3-hydroxyphenyl)ethyl, 2-(3,5-dihydroxyphenyl)ethyl, (3-methoxyphenyl)methoxy, 2-[3-(methylcarbamoyl)phenyl]methoxy, 2-[3-methoxy-5-(methylcarbamoyl)phenyl]methoxy, 2-[3-(methylcarbamoyl)phenyl]ethyl, 2-[3-methoxy-5-(methylcarbamoyl)phenyl]ethyl, (3-hydroxyphenyl)methoxy, (3,5-dihydroxyphenyl)methoxy, (3-methoxyphenyl)methoxy, (3-chloro-5-methoxy-phenyl)methoxy, 2-(2,6-dimethoxypyridin-4-yl)ethyl, 2-(5-fluoro-2-methoxy-pyridin-4-yl)ethyl, (3-methoxy-5-methyl-phenyl)methoxy, (3-fluorophenyl)methoxy, (3-chlorophenyl)methoxy, 2-(3-aminophenyl)ethyl, 2-(5-methoxythiophen-2-yl)ethyl, 2-(2-furyl)ethyl, (2,6-dimethoxypyridin-4-yl)methoxy or a 2-(3-chloro-5-methoxy-phenyl)ethyl group.

In a further additional aspect of the invention R1 represents a 2-(3-methoxyphenyl)ethyl, 2-(3,5-dimethoxyphenyl)ethyl, 2-propoxy, (3,5-dimethoxyphenyl)methoxy, 2-(3-hydroxyphenyl)ethyl, or a (3-fluorophenyl)methoxy group.

In another embodiment of the invention, R2 represents hydrogen or a C1-C3 alkyl group (such as methyl, ethyl, n-propyl, or isopropyl).

In a further aspect of the invention, R2 represents hydrogen or methyl.

In a further aspect of the invention, R2 represents hydrogen.

In a further embodiment of the invention, R3 represents a C1-C3 alkyl group; a C3-C5 cycloalkyl group; or a -CONH2 group.

In a further embodiment of the invention, R3 represents a C1-C3 alkyl group; a C3-C5 cycloalkyl group.

In a further aspect of the invention, R3 represents methyl, ethyl, propyl, 2-propyl, cyclopropyl, cyclobutyl or -CONH2.

In a further aspect of the invention, R3 represents methyl, ethyl, propyl, 2-propyl or cyclopropyl or cyclobutyl.
In a further aspect of the invention R³ represents methyl, cyclopropyl or cyclobutyl.
In a further aspect of the invention R³ represents methyl, cyclopropyl.
In a further aspect of the invention R³ represents methyl.
In a further aspect of the invention R³ represents cyclopropyl.

In a further embodiment of the invention R⁴ represents hydrogen, a Ci-C₆alkyl group; a C₃-C₅cycloalkyl; a Ci-C₆alkoxy group.

In a further aspect of the invention, R⁴ represents hydrogen, methyl or methoxy.
In a further aspect R⁴ represents hydrogen.

In an embodiment of the invention, there is provided a subset of compounds of formula (I), and pharmaceutically acceptable salts thereof, in which:

\[
\begin{align*}
R^1 & \text{ represents } \text{a Ci-C₆alkyl optionally substituted by one or more R}^{13}, \\
& \text{a C₃-C₅cycloalkyl optionally substituted by one or more R}^{14}, \\
& \text{a 4- to 6-membered heterocyclyl group optionally substituted by one or more R}^{16}, \\
& \text{a Ci-C₆alkoxy group optionally substituted by one or more R}^{17}, \\
& \text{a C₆-aryloxy group optionally substituted by one or more R}^{18}, \\
& \text{a 5- to 6-membered heteroaryloxy group optionally substituted by one or more R}^{19}, \text{ or} \\
& -A-B;
\end{align*}
\]

wherein

\[
\begin{align*}
A\ &\text{ represents } \text{a C2-alkylene optionally substituted by one or more R}^{20}, \text{ a Ci-alkyleneoxy optionally substituted by one or more R}^{21}, \text{ or a oxyCi-alkylene optionally substituted by one or more R}^{22}; \text{ and} \\
B\ &\text{ represents } \text{a 5- or 6-membered aromatic ring} \text{ optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the aromatic ring being optionally substituted by one or more R}^{23} \text{ and optionally wherein two or more adjacent R}^{23} \text{ together with the atoms to which they are attached form a partially or fully unsaturated 4- to 6-membered ring;} \\
R^2 & \text{ represents hydrogen;}
\end{align*}
\]
R³ represents methyl, ethyl, propyl, i-propyl, cyclopropyl or cyclobutyl; and
R⁴ represents hydrogen.

In another embodiment of the invention, there is provided a subset of compounds of
formula (I), and pharmaceutically acceptable salts thereof, in which:

5  R¹ represents a C₁-C₆ alkyl optionally substituted by one or more R¹³,
a 4- to 6-membered heterocyclyl group optionally substituted by one or
more R¹⁶,
a C₁-C₆ alkoxy group optionally substituted by one or more R¹⁷,
a C₆-aryloxy group optionally substituted by one or more R¹⁸,
a 5- to 6-membered heteroaryloxy group optionally substituted by one
or more R¹⁹, or
-A-B;

wherein

A represents a C₂-alkylene optionally substituted by one or more R²⁰, a Q-alkyleneoxy optionally
substituted by one or more R²¹, or a oxyC₁-alkylene
optionally substituted by one or more R²²; and

B represents a 5- or 6-membered aromatic ring
optionally comprising at least one ring heteroatom
selected from nitrogen, oxygen and sulphur, the

10 aromatic ring being optionally substituted by one or
more R²³ and optionally wherein two or more adjacent
R²³ together with the atoms to which they are attached
form a partially or fully unsaturated 4- to 6-membered
ring;

15 R² represents hydrogen;

R³ represents methyl, ethyl, propyl, i-propyl, cyclopropyl or cyclobutyl; and
R⁴ represents hydrogen.

In another embodiment of the invention, there is provided a subset of compounds of
formula (I), and pharmaceutically acceptable salts thereof, in which:

20 R¹ represents a C₁-C₆ alkyl group substituted by one or more substituents selected
from hydroxyl and C₁-C₆ alkoxy which may be optionally substituted
by one or more substituents selected from halogen, C₁-C₆ alkyl,
Ci-C<sub>6</sub>alkoxy, Ci-C<sub>6</sub>alkylthio, amino (-NH<sub>2</sub>), mono- and di-
ci-C<sub>6</sub>alkylamino, cyano, hydroxyl and trifluoromethyl,
a Ci-C<sub>6</sub>alkoxy group optionally substituted by one or more R<sub>17</sub>,
a C<sub>6</sub>-aryloxy group optionally substituted by one or more R<sub>18</sub>,
a 5- to 6-membered heteroaryloxy group optionally substituted by one
or more R<sub>19</sub>, or
-A-B;
wherein A represents a C2-alkylene optionally substituted by
one or more R<sub>20</sub>, a Ci-alkyleneoxy optionally
substituted by one or more R<sub>21</sub>, or a oxyCi-alkylene
optionally substituted by one or more R<sub>22</sub>; and
B represents a 5- or 6-membered aromatic ring
optionally comprising at least one ring heteroatom
selected from nitrogen, oxygen and sulphur, the
aromatic ring being optionally substituted by one or
more R<sub>23</sub> and optionally wherein two or more adjacent
R<sub>23</sub> together with the atoms to which they are attached
form a partially or fully unsaturated 4- to 6-membered
ring;
R<sup>2</sup> represents hydrogen;
R<sup>3</sup> represents methyl, ethyl, propyl, i-propyl, cyclopropyl or cyclobutyl; and
R<sup>4</sup> represents hydrogen.
In another embodiment of the invention, there is provided a subset of compounds of
formula (I), and pharmaceutically acceptable salts thereof, in which:
R<sup>1</sup> represents a Ci-C<sub>6</sub>alkyl group substituted by one or more substituents selected
from hydroxyl and Ci-C<sub>6</sub>alkoxy which may be optionally substituted
by one or more substituents selected from halogen, Ci-C<sub>6</sub>alkyl,
Ci-C<sub>6</sub>alkoxy, Ci-C<sub>6</sub>alkylthio, amino (-NH<sub>2</sub>), mono- and di-
ci-Cealkylamino, cyano, hydroxyl and trifluoromethyl,
a Ci-C<sub>6</sub>alkoxy group optionally substituted by one or more R<sub>17</sub>,
a C<sub>6</sub>-aryloxy group optionally substituted by one or more R<sub>18</sub>,
a 5- to 6-membered heteroaryloxy group optionally substituted by one or more $R^{19}$, or
-A-B;
wherein

A represents a C2-alkylene optionally substituted by one or more $R^{20}$, or a oxyC2-alkylene optionally substituted by one or more $R^{22}$; and
B represents a 5- or 6-membered aromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the aromatic ring being optionally substituted by one or more $R^{23}$;

$R^2$ represents hydrogen;
$R^3$ represents methyl, ethyl, propyl, i-propyl, cyclopropyl or cyclobutyl; and
$R^4$ represents hydrogen.

In an embodiment of the invention, there is provided a subset of compounds of formula (I), and pharmaceutically acceptable salts thereof, in which:

$R^1$ represents a Ci-C$_3$alkyl group substituted by one or more substituents selected from hydroxyl and Ci-C$_3$alkoxy which may be optionally substituted by one or more substituents selected from halogen, Ci-C$_3$alkyl and Ci-C$_3$alkoxy,
a Ci-C$_3$alkoxy group optionally substituted by one or more substituents selected from Ci-C$_3$alkoxy and cyclopropyl,
a phenoxy group optionally substituted by one or more substituents selected from Ci-C$_3$alkyl, Ci-C$_3$alkoxy and cyclopropyl, or
-A-B wherein A represents a C2-alkylene, and B represents a phenyl ring wherein the phenyl ring may be optionally substituted by one or more $R^{23}$;

$R^2$ represents hydrogen or methyl;
$R^3$ represents methyl, ethyl, propyl, i-propyl or cyclopropyl; and
$R^4$ represents hydrogen.

In an embodiment of the invention, there is provided a subset of compounds of formula (I), and pharmaceutically acceptable salts thereof, in which:
R\textsuperscript{1} represents a Ci-C\textsubscript{3} alkyl group substituted by one or more substituents selected from hydroxyl and Ci-C\textsubscript{3} alkoxy which may be optionally substituted by one or more substituents selected from halogen, Ci-C\textsubscript{3} alkyl and Ci-C\textsubscript{3} alkoxy,

a Ci-C\textsubscript{3} alkoxy group optionally substituted by one or more substituents selected from Ci-C\textsubscript{3} alkoxy and cyclopropyl,
a phenoxy group optionally substituted by one or more substituents selected from Ci-C\textsubscript{3} alkyl, Ci-C\textsubscript{3} alkoxy and cyclopropyl, or

-A-B wherein A represents a C\textsubscript{2}-alkylene, and B represents a pyridine-4-yl ring wherein the pyridin-4-yl ring may be optionally substituted by one or more R\textsuperscript{23};

R\textsuperscript{2} represents hydrogen or methyl;
R\textsuperscript{3} represents methyl, ethyl, propyl, i-propyl or cyclopropyl; and
R\textsuperscript{4} represents hydrogen.

In an embodiment of the invention, there is provided a subset of compounds of formula (I), and pharmaceutically acceptable salts thereof, in which:

R\textsuperscript{1} represents a Ci-C\textsubscript{3} alkyl group substituted by one or more substituents selected from hydroxyl and Ci-C\textsubscript{3} alkoxy which may be optionally substituted by one or more substituents selected from halogen, Ci-C\textsubscript{3} alkyl and Ci-C\textsubscript{3} alkoxy,
a Ci-C\textsubscript{3} alkoxy group optionally substituted by one or more substituents selected from Ci-C\textsubscript{3} alkoxy and cyclopropyl,
a phenoxy group optionally substituted by one or more substituents selected from Ci-C\textsubscript{3} alkyl, Ci-C\textsubscript{3} alkoxy and cyclopropyl, or

-A-B wherein A represents an oxyCi-alkylene, and B represents a phenyl ring or a pyridin-4-yl ring wherein the phenyl or pyridin-4-yl ring may be optionally substituted by one or more R\textsuperscript{23};

R\textsuperscript{2} represents hydrogen or methyl;
R\textsuperscript{3} represents methyl, ethyl, propyl, i-propyl or cyclopropyl; and
R\textsuperscript{4} represents hydrogen.

In a further aspect of the invention, there is provided a compound of formula (I) (as depicted above) wherein:
R\(^1\) represents a hydroxymethyl, methoxypropyl, ethoxypropyl, phenylethyl, 2-(3-methoxyphenyl)ethyl, 2-(3,5-dimethoxyphenyl)ethyl, \(\beta\)-propxoy, benzyloxy, (3,5-dimethoxyphenyl)methoxy, 2-(3-hydroxyphenyl)ethyl, 2-(3,5-dihydroxyphenyl)ethyly, (3-methoxyphenyl)methoxy,

5 [3-(methylcarbamoyl)phenyl]methoxy, [3-methoxy-5-(methylcarbamoyl)phenyl]methoxy, 2-[3-(methylcarbamoyl)phenyl] ethyl, 2-[3-methoxy-5-(methylcarbamoyl)phenyl] ethyl, (3-hydroxyphenyl)methoxy, (3,5-dihydroxyphenyl)methoxy,

10 (3-chloro-5-methoxy-phenyl)methoxy, 2-(2,6-dimethoxy-pyridin-4-yl)ethyl, (5-fluoro-2-methoxy-pyridin-4-yl)methoxy, 2-(5-fluoro-2-methoxy-pyridin-4-yl)ethyl, (3-methoxy-5-methyl-phenyl)methoxy, (3-fluorophenyl)methoxy,

15 (3-chlorophenyl)methoxy, 2-(3-aminophenyl)ethyl, 2-(5-methoxythiophen-2-yl)ethyl, 2-(2-furyl)ethyl, (2,6-dimethoxy-pyridin-4-yl)methoxy or a 2-(3-chloro-5-methoxy-phenyl)ethyl group;

R\(^2\) represents hydrogen;

R\(^3\) represents methyl, cyclopropyl, or cyclobutyl; and

R\(^4\) represents hydrogen, or a pharmaceutically acceptable salt thereof.

In a further aspect of the invention, there is provided a compound of formula (I) (as depicted above) wherein:

25 R\(^1\) represents a 2-(3-methoxyphenyl)ethyl, 2-(3,5-dimethoxyphenyl)ethyl, \(\beta\)-propxoy, (3,5-dimethoxyphenyl)methoxy, 2-(3-hydroxyphenyl)ethyl, or (3-fluorophenyl)methoxy group;

R\(^2\) represents hydrogen;

R\(^3\) represents methyl; and

R\(^4\) represents hydrogen, or a pharmaceutically acceptable salt thereof.

Examples of compounds of the invention include:
N-[(5-methyl-1,2-oxazol-3-yl)methyl]-N'-(5-propan-2-yloxy-2H-pyrazol-3-yl)pyrimidine-2,4-diamine;
N'-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-N-[(5-methyl-1,2-oxazol-3-yl)methyl]pyrimidine-2,4-diamine;
N'-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-N-[(5-methyl-1,2-oxazol-3-yl)methyl]pyrimidine-2,4-diamine;
N'-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-N-[(5-methyl-1,2-oxazol-3-yl)methyl]pyrimidine-2,4-diamine;
3-[2-[[5-methyl-1,2-oxazol-3-yl]methylamino]pyrimidin-4-yl]amino]-1H-pyrazol-3-yl]ethyl]phenol; and
N'-[5-[(3-fluorophenyl)methoxy]-2H-pyrazol-3-yl]-N-[(5-methyl-1,2-oxazol-3-yl)methyl]pyrimidine-2,4-diamine,
and pharmaceutically acceptable salts and solvates of any one thereof.

In another aspect of the invention, particular compounds of the invention are any one of the Examples or pharmaceutically acceptable salts of any one thereof.

In a further aspect of the invention, there is provided a compound selected from any one of the Examples.

The present invention further provides a process for the preparation of a compound of formula (I) as defined herinbefore above, or a pharmaceutically acceptable salt thereof, which comprises:

(i) reacting a compound of formula (IV)
wherein X represents a leaving group (e.g. halogen or sulfanyl such as
methanesulfanyl or sulphonyloxy such as methanesulphonyloxy or
toluene-4-sulphonyloxy), Z represents hydrogen or a halogen, and R¹ and R⁴ are as
hereinbefore defined for a compound formula (I)
with a compound of formula (V)

wherein R² and R³ are as defined hereinbefore for a compound of formula (I)
to give,
when Z is hydrogen, a compound of formual (I) or,
when Z is halogen, a compound of formula (VI)

and (ii) when Z is a halogen, optionally reacting a compound of formula (VI) with a de-
halogenating reagent to give a compound of formula (I);
and optionally after (i) or (ii) carrying out one or more of the following:
• converting the compound obtained to a further compound of the invention
• forming a pharmaceutically acceptable salt of the compound.
Step (i) may conveniently be carried out in a suitable solvent such as 2-
methoxyethanol, 1-methylpyrrolidinone, butanol or dimethylacetamide at a temperature in the range from 90-200°C, optionally with microwave irradiation. The reaction can be carried out in the presence or absence of a suitable acid or base 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) or an inorganic base such as sodium carbonate, or an organic base such as 7V,7V-diisopropylethylamine.

Optional dehalogenation may conveniently be carried out in a suitable solvent such as ethanol in the presence of a suitable catalyst such as 5-20% palladium on carbon under an atmosphere of hydrogen.

Compounds of formula (IV) may be prepared by reacting a compound of formula (II)

\[
\begin{align*}
\text{R}^1 \\
\text{H} \quad \text{N} \\
\text{N} \\
\text{NH}_2
\end{align*}
\]

(II)

wherein \( \text{R}^1 \) is as defined hereinbefore for a compound of formula (I), with a compound of formula (III),

\[
\begin{align*}
\text{Z} \\
\text{Y} \\
\text{X} \\
\text{Y} \\
\text{X}
\end{align*}
\]

(III)

wherein \( \text{X} \) and \( \text{Y} \) each independently represents a leaving group (e.g. halogen or sulfanyl such as methanesulfanyl or sulphonyloxy such as methanesulphonyloxy or toluene-4-sulphonyloxy), \( \text{Z} \) represents hydrogen or a halogen, and \( \text{R}^4 \) is as defined hereinbefore for a compound of formula (I) to give a compound of formula (IV)
This reaction may conveniently be carried out in the presence of a suitable solvent such as ethanol, butanol, toluene or 1-methylpyrrolid-2-one, optionally in the presence of a suitable acid or base 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) or an inorganic base such as sodium carbonate, or an organic base such as 7V,7V-diisopropylethylamine and at a temperature in the range from 0°C to reflux.

In a further aspect of the present invention there is provide a process for the preparation of a compound of formula (I) as defined hereinbefore above, or a pharmaceutically acceptable salt thereof, which comprises:

reacting a compound of formula (IX),

wherein Y is a leaving group such as chloro, and R², R³ and R⁴ are as defined hereinbefore for a compound of formula (I), with a compound of formula (II)

wherein R¹ is as defined hereinbefore for a compound of formula (I)
and optionally carrying out one or more of the following:

- converting the compound obtained to a further compound of the invention
- forming a pharmaceutically acceptable salt of the compound.

The process may conveniently be carried out in a suitable solvent such as 1-methylpyrrolidinone or dimethylacetamide in the presence of a suitable acid such as hydrogen chloride in dioxane at a temperature in the range from 90 to 120°C.

Compounds of Formula (IX) may be prepared by

(a) reacting a compound of formula (VII)

\[
\begin{align*}
\text{R}^4 \quad \text{N} \\
\text{O} \\
\text{N} \quad \text{X}
\end{align*}
\]

(VII)

wherein \( \text{R}^4 \) is as defined hereinbefore for a compound of formula (I) and \( \text{X} \) represents a leaving group (e.g. halogen or sulfanyl such as methanesulfanyl or sulphonyloxy such as methanesulphonyloxy or toluene-4-sulphonyloxy),

with a compound of formula (V)

\[
\begin{align*}
\text{HN} \\
\text{R}^2 \\
\text{R}^3
\end{align*}
\]

(V)

wherein \( \text{R}^2 \) and \( \text{R}^3 \) are as defined hereinbefore for a compound of formula (I)

to give a compound of formula (VIII)

\[
\begin{align*}
\text{R}^4 \quad \text{N} \\
\text{O} \\
\text{N} \quad \text{R}^2 \\
\text{N} \\
\text{R}^3
\end{align*}
\]

(VIII)
and,

(b) by reacting a compound of formula (VIII) with a chlorinating agent to a compound of formula (IX)

\[
\begin{align*}
\text{R}^4 & \quad \text{N} \quad \text{N} \\
\text{Y} & \quad \text{N} \quad \text{N} \\
\text{R}^2 & \quad \text{O} \\
\text{R}^3 & 
\end{align*}
\]

(IX)

wherein Y is a leaving group such as chloro.

Step (a) may conveniently be carried out in a suitable solvent such as diglyme in the presence of a suitable base such as 7V,7V-diisopropylethylamine at a temperature in the range from 120 to 180°C.

Step (b) may conveniently be carried out in a suitable solvent such as toluene with a suitable chlorinating agent such as phosphorus oxychloride in the presence of a suitable base such as 7V,7V-diisopropylethylamine at a temperature in the range from 60 to 100°C.

In a still further aspect of the present invention there is provided a process for the preparation of a compound of formula (I) as hereinbefore defined but wherein R4 represent a Ci-C6alkoxy group optionally substituted with d-C3alkoxy, hydroxyl, amino (-NH2), mono-C3alkyamino and di-(C3alky)amino, -NR1R11, or -S(O)2R12, or a pharmaceutically acceptable salt thereof, which comprises:

reacting a compound of formula (XII)

\[
\begin{align*}
\text{R}^1 & \quad \text{N} \quad \text{N} \\
\text{A} & \quad \text{N} \quad \text{N} \\
\text{R}^2 & \quad \text{O} \\
\text{R}^3 & 
\end{align*}
\]

(XII)

with a compound of formula (XIII)
H·R₄
(XIII)

wherein R₄ represents a Ci-C₆alkoxy group optionally substituted with Ci-C₃alkoxy, hydroxyl, amino (-NH₂), mono-Ci-C₃alkyamino and di-(Ci-C₃alky)amino, -NR₁₀R₁₁, or -S(O)ₚR₁₂ wherein y=0, and when R₄ is -S(O)ₚR₁₂ wherein y=0, optionally reacting with an oxidising agent, and optionally carrying out one or more of the following:

• converting the compound obtained to a further compound of the invention
• forming a pharmaceutically acceptable salt of the compound.

The reaction may conveniently be carried out in a suitable solvent such as 1-methylpyrrolidinone, dimethylacetamide or a compound of formula (XIII) used as solvent in the presence of a suitable base such as 7V,7V-diisopropylethylamine or sodium hydride at a temperature in the range from 80 to 200°C, optionally with microwave irradiation.

The compound of formula (XII) may be obtained by:

1. reacting a compound of formula (X)

   ![Diagram](attachment:image.png)

   (X)

wherein X, Y and A each independently represents a leaving group (such as halogen or sulfanyl such as methanesulfanyl or sulphonyloxy such as methanesulphonyloxy or toluene-4-sulphonyloxy), with a compound of formula (II),

![Diagram](attachment:image.png)

(H)

wherein R¹ is as defined hereinbefore for a compound of formula (I) to give a compound of formula (XI)
and,

(2) reacting a compound of formula (XI) with a compound of formula (V)

wherein \( R_2 \) and \( R_3 \) are as defined hereinbefore for a compound of formula (I) to give a compound of formula (XII)

Step (1) may conveniently be carried out in a suitable solvent such as ethanol in the presence of a suitable base such as sodium carbonate or 7V,7V-diisopropylethylamine at a temperature in the range from 0 to 25°C.

Step (2) may conveniently be carried out in a suitable solvent such as butanol, hexanol, 1-methylpyrrolidinone or dimethylacetamide in the presence of a suitable base such as 7V,7V-diisopropylethylamine at a temperature in the range from 80 to 120°C.

Compounds of formulae (II), (III), (V), (VII), (X) and (XIII) are either commercially available, are known in the literature or may be prepared using known techniques.

Compounds of formula (I) can be converted into further compounds of formula (I) using standard procedures. Examples of the types of conversion reactions that may be used include introduction of a substituent by means of an aromatic substitution reaction, reduction
of substituents, alkylation of substituents, de-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 reduction reactions include the reduction of a nitro group to an amino group by catalytic hydrogenation with a nickel catalyst or by treatment with iron in the presence of hydrochloric acid with heating or the reduction of a cyano group to an amino group by treatment with lithium aluminium hydride; particular examples of de-alkylation reactions include the conversion of a methoxy group to a hydroxyl by treatment with boron tribromide; and particular examples of oxidation reactions include oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or/?-toluenesulphonate, or an alkali metal salt such as a sodium or potassium salt.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers (including atropisomers) of the compounds of formula (I) and mixtures thereof including racemates.
Certain compounds of formula (I) are capable of existing in tautomeric forms. For example, N’-[5-[(3-fluorophenyl)methoxy]-2H-pyrazol-3-yl]-N-[(5-methyl-1,2-oxazol-3-yl)methyl]pyrimidine-2,4-diamine may also exist as the corresponding tautomer N’-[5-[(3-fluorophenyl)methoxy]-1H-pyrazol-3-yl]-N-[(5-methyl-1,2-oxazol-3-yl)methyl]pyrimidine-2,4-diamine.

It is understood that compounds referred to by name, unless otherwise stated, include all tautomers of the compound.

The use of tautomers and mixtures thereof also form an aspect of the present invention.

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators or inhibitors of FGFR activity, and may be used in the treatment of proliferative and hyperproliferative diseases/conditions, examples of which include the following cancers:

1. Carcinoma, including that of the bladder, brain, breast, colon, kidney, liver, lung, ovary, pancreas, prostate, stomach, cervix, colon, thyroid and skin;
2. Hematopoietic tumors of lymphoid lineage, including acute lymphocytic leukaemia, B-cell lymphoma and Burketts lymphoma;
hematopoietic tumours of myeloid lineage, including acute and chronic myelogenous leukaemias and promyelocytic leukaemia;

(4) tumours of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; and

(5) other tumours, including melanoma, seminoma, tetratocarcinoma, neuroblastoma and glioma.

The compounds of the invention are especially useful in the treatment of tumors of the breast and prostate.

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention also provides a method of treating cancer which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined.

The invention still further provides a method of modulating FGFR activity which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined.

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt thereof, are effective anti-cancer agents which property is believed to arise from their FGFR inhibitory properties. Accordingly the compounds of the present invention are expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by FGFR, i.e. the compounds may be used to produce a FGFR inhibitory effect in a warm-blooded animal in need of such treatment.

Thus the compounds of the present invention provide a method for treating cancer characterised by inhibition of FGFR, i.e. the compounds may be used to produce an anti-cancer effect mediated alone or in part by the inhibition of FGFR.
Such a compound of the invention is expected to possess a wide range of anti-cancer properties as activating mutations in FGFR have been observed in many human cancers, including but not limited to, melanoma, papillary thyroid tumours, cholangiocarcinomas, colon, ovarian and lung cancers. Thus it is expected that a compound of the invention will possess anti-cancer activity against these cancers. It is in addition expected that a compound of the present invention will possess activity against a range of leukaemias, lymphoid malignancies and solid tumours such as carcinomas and sarcomas in tissues such as the liver, kidney, bladder, prostate, breast and pancreas. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the breast and prostate. More particularly such compounds of the invention, or a pharmaceutically acceptable salt thereof, are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with FGFR, especially those tumours which are significantly dependent on FGFR for their growth and spread, including for example, certain tumours of the breast and prostate.

Thus according to this aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use as a medicament.

According to a further aspect of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of a FGFR inhibitory effect in a warm-blooded animal such as man.

According to this aspect of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm-blooded animal such as man.

According to a further feature of the invention, there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as defined herein before in the manufacture of a medicament for use in the treatment of melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries.
According to a further aspect of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the production of a FGFR inhibitory effect in a warm-blooded animal such as man.

According to this aspect of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the production of an anti-cancer effect in a warm-blooded animal such as man.

According to a further feature of the invention, there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as defined herein before in the treatment of melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries.

According to a further feature of this aspect of the invention there is provided a method for producing a FGFR inhibitory 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 defined above.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-cancer 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 defined above.

According to an additional feature of this aspect of the invention there is provided a method of treating melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries, 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 defined herein before.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or
carrier for use in the production of a FGFR inhibitory effect in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the production of an anti-cancer effect in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of melanoma, papillary thyroid tumours, cholangiocarcinomas, colon cancer, ovarian cancer, lung cancer, leukaemias, lymphoid malignancies, carcinomas and sarcomas in the liver, kidney, bladder, prostate, breast and pancreas, and primary and recurrent solid tumours of the skin, colon, thyroid, lungs and ovaries in a warm-blooded animal such as man.

The compounds of formula (I) and pharmaceutically acceptable salts thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the skin or to the lung and/or airways) in the form, e.g., of creams, solutions, suspensions,
heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral
administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral
administration in the form of solutions or suspensions; or by subcutaneous administration; or
by rectal administration in the form of suppositories; or transdermally.

The compositions of the invention may be obtained by conventional procedures using
conventional pharmaceutical excipients, well known in the art. Thus, compositions intended
for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or
preservative agents.

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

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

Aqueous suspensions generally contain the active ingredient in finely powdered form
together with one or more suspending agents, such as sodium carboxymethylcellulose,
methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum
tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation
products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or
condensation products of ethylene oxide with long chain aliphatic alcohols, for example
heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters
derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or
condensation products of ethylene oxide with long chain aliphatic alcohols, for example
heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters
derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or
condensation products of ethylene oxide with partial esters derived from fatty acids and 
hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions 
may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, 
anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening 
agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a 
vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such 
as liquid paraffin). The oily suspensions may also contain a thickening agent such as 
beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and 
flavouring agents may be added to provide a palatable oral preparation. These compositions 
may be preserved by the addition of an anti-oxidant such as ascorbic acid.

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

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

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

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

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30µ or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

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

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

The size of the dose for therapeutic purposes of a compound of the invention will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In general, a compound of the invention will be administered so that a daily dose in the range, for example, from 0.5 mg to 75 mg active ingredient per kg body weight is received, given if required in divided doses. In general lower doses will be administered when
a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, from 0.5 mg to 30 mg active ingredient per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, from 0.5 mg to 25 mg active ingredient per kg body weight will generally be used.

Oral administration is however preferred. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active ingredient.

For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The anti cancer treatment defined hereinbefore 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) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and 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 polokinase inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and idoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5*-reductase such as finasteride;
(iii) anti-invasion agents (for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341) and N-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide (dasatinib, BMS-354825; J. Med. Chem., 2004, 47, 6658-6661), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase);

(iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti erbB2 antibody trastuzumab [Herceptin™], the anti-EGFR antibody panitumumab, the anti erbB1 antibody cetuximab [Erbitux, C225] and any growth factor or growth factor receptor antibodies disclosed by Stern et al. Critical reviews in oncology/haematology, 2005, Vol. 54, pp 11-29); such inhibitors also include tyrosine 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, ZD 1839), 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), erbB2 tyrosine kinase inhibitors such as lapatinib, inhibitors of the hepatocyte growth factor family, inhibitors of the platelet-derived growth factor family such as imatinib, inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006)), inhibitors of cell signalling through MEK and/or AKT kinases, inhibitors of the hepatocyte growth factor family, c-kit inhibitors, abl kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1 152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

(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™) and VEGF receptor tyrosine kinase inhibitors such as A-

(4-bromo-2-fluoroanilino)-6-methoxy-7-(l-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474; Example 2 within WO 01/32651), 4-(4-fluoro-2-methylindol-5-yl)oxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212),
vatalanib (PTK787; WO 98/35985) and SUl 1248 (sunitinib; WO 01/60814), compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin avb3 function and angiotatin));

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

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

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

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 within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

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

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.
Examples

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

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

(ii) organic solutions were dried over anhydrous sodium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30mmHg) with a bath temperature of up to 60 °C;

(iii) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(iv) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectral data;

(v) 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 parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 400 MHz or 300 MHz using perdeuterio dimethyl sulphoxide (DMSOd6) as solvent unless otherwise indicated;

(viii) chemical symbols have their usual meanings; SI units and symbols are used;

(ix) mass spectra (MS) data was generated on an LC/MS system where the HPLC component comprised generally either an Agilent 1100 or Waters Alliance HT (2790 & 2795) equipment and was run on a Phenomenex Gemini C18 5μm, 50 x 2 mm column (or similar) eluting with either acidic eluent (for example, using a gradient between 0 - 95% water / acetonitrile with 5% of a 1% formic acid in 50:50 water:acetonitrile (v/v) mixture; or using an equivalent solvent system with methanol instead of acetonitrile), or basic eluent (for example, using a gradient between 0 - 95% water / acetonitrile with 5% of a 0.1% 880 Ammonia in acetonitrile mixture); and the MS component comprised generally a Waters ZQ spectrometer.

Chromatograms for Electrospray (ESI) positive and negative Base Peak Intensity, and UV Total Absorption Chromatogram from 220-3 O0nm, are generated and values for m/z are given; generally, only ions which indicate the parent mass are reported and unless otherwise
stated the value quoted is the (M+H)+ for positive ion mode and (M-H)- for negative ion mode;

(x) Preparative HPLC was performed on C18 reversed-phase silica, for example on a Waters 'Xterra' preparative reversed-phase column (5 microns silica, 19 mm diameter, 100 mm length) using decreasingly polar mixtures as eluent, for example decreasingly polar mixtures of water (containing 1% acetic acid or 1% aqueous ammonium hydroxide (d=0.88) and acetonitrile;

(xi) where a synthesis is described as being analogous to that described in a previous example the amounts used are the millimolar ratio equivalents to those used in the previous example;

(xii) the following abbreviations have been used:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>DMF</td>
<td>7V,7V-dimethylformamide;</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate;</td>
</tr>
<tr>
<td>Pd$_2$(dba)$_3$</td>
<td>tris(dibenzylideneacetone)dipalladium (0);</td>
</tr>
<tr>
<td>BINAP</td>
<td>(+/-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl;</td>
</tr>
<tr>
<td>Pd(Ph$_3$P)$_4$</td>
<td>tetrakis(triphenylphosphine)palladium(0);</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid;</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulphoxide;</td>
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<tr>
<td>DIPEA</td>
<td>7V,7V,-diisopropylethylamine or N-ethyl-N-propan-2-yl-propan-2-amine;</td>
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<tr>
<td>HATU</td>
<td>$N$,$N$,$N$,$N'$-tetramethyl-O-(7-azabenzotriazol-1-yl)uranium; hexafluorophosphate;</td>
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<tr>
<td>DME</td>
<td>1,2-dimethoxy ethane;</td>
</tr>
<tr>
<td>DMA</td>
<td>7V,7V,-dimethylacetamide;</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol; and</td>
</tr>
<tr>
<td>NEt$_3$</td>
<td>triethylamine;</td>
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</table>
and (xii) "Gilson HPLC" refers to a YMC-AQC 18 reverse phase HPLC Column with dimension 20mm/100 and 50mm/250 in water-CH\textsubscript{3}CN with 0.1% TFA, 10mM ammonium acetate, or 0.1% formic acid as mobile phase, obtained from Waters Corporation 34, Maple street, Milford, MA, USA.

Table 1

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<tr>
<th>Example</th>
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<td>5</td>
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Example 1
N-[(5-methyl-1,2-oxazol-3-yl)methyl]-N^r-(5-propan-2-yloxy-2H-pyrazol-3-yl)pyrimidine-
2,4-diamine

To a solution of 2-chloro-N-(5-propan-2-yloxy-2H-pyrazol-3-yl)pyrimidin-4-amine (100mg, 0.39mmol, leq) dissolved in 2-methoxyethanol (3ml) (in a microwave tube) was added (5-methyl-1,2-oxazol-3-yl)methanamine (53mg, 0.47mmol, 1.2 eq). The mixture was heated to 200°C in a microwave reactor for 30 mins. The solvent was removed under vacuum and the residue dissolved in water and a couple of drops of cone, aq ammonia was added to bring to reaction mixture to basic pH. The resulting solid product was filtered off, washed with water and dried under vacuum to give the title compound as a pale orange solid (114mg, 88% yield).

^1H NMR (499.803 MHz, DMSO, Sample was heated 373K) δ 1.27 (6H, d), 2.37 (3H, s), 4.49 (2H, d), 4.59-4.67 (IH, m), 5.27 (IH, bs), 6.01-6.13 (2H, m), 7.22 (IH, bs), 7.90 (IH, d), 9.48 (IH, bs), 11.45 (IH, bs) MS:m/z 330 (MH+). Kinase: 0.16μM.

2-chloro-N-(5-propan-2-yloxy-2H-pyrazol-3-yl)pyrimidin-4-amine, used as starting material above, was prepared as follows:-

2,4-Dichloropyrimidine (10.05 lg, 67.0mmol.leq) and 5-propan-2-yloxy-2H-pyrazol-3-amine, (10.00g, 70.0mmol, 1.05eq) were mixed together in ethanol (100ml) and stirred at 60°C under nitrogen atmosphere for 4 days. The reaction mixture was reduced in vacuo and the residue was dissolved in ethyl acetate (200ml) and washed with water (200ml) followed by brine (100ml). The ethyl acetate layer was dried over MgSO4 and filtered, reduced under vacuum to leave a crude, pale yellow oil. Purification by silica column chromatography (eluting with a mixture of dichloromethane 95%/methanol 5% to dichloromethane 90%/methanol 10%) and evaporation of the appropriate fractions gave an oily solid. The oily solid was dissolved in hot
diethyl ether (100ml) and left to stand whereupon a white solid crystallised out. This was filtered off and washed with ether (10ml) and dried to give a white crystalline solid. This was one of the impurities. The filtrate was reduced in vacuo and dissolved in a mixture of 50% hot methanol in diethyl ether. A solid slowly crystallised out which was filtered off, washed with a mixture of 50% methanol in diethyl ether (100ml), and dried to give the title compound as a white solid (5.003g, 29% yield).

1H NMR (500.133 MHz, DMSO @373K, d4 Acetic Acid) δ 1.31 (6H, d), 4.47 - 4.54 (IH, m), 5.61 (H, s), 6.97 (IH, d), 8.10 (IH, d)

MS: m/z 254 (MH+).

5-propan-2-yloxy-2H-pyrazol-3-amine, used as starting material, can be prepared according to the literature (Sato, Tadahisa; Mizukawa, Hiroki; Kawagishi, Toshio. Preparation of 3-alkoxy-5-amino-1H-pyrazoles as intermediates for photographic magenta couplers JP01013072).

Example 2

N’-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]methyl]pyrimidine-2,4-diamine

4-chloro-N’-[5-(methyl-1,2-oxazol-3-yl)methyl]pyrimidin-2-amine (120 mg, 0.534 mmol, 1.0 eq) was dissolved in ethanol (5 ml), 5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-amine (116 mg, 0.534 mmol, 1 eq) was added and the mixture was stirred at 80 ºC for 24 h. The reaction mixture was cooled to room temperature and the precipitate collected by filtration. The precipitate was dissolved in water (10 ml) and a drop of concentrated ammonia solution was added. The precipitate was collected by filtration, washed with water and dried in vacuo to yield N’-[5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-N’-[5-(methyl-1,2-oxazol-3-yl)methyl]pyrimidine-2,4-diamine (159 mg, 74%) as a white solid.

1H NMR (399.902 MHz, DMSO) δ 2.35 (s, 3H), 2.87 (m, 4H), 3.73 (s, 3H), 4.49 (d, J = 5.8 Hz, 2H), 6.14 (s, IH), 6.34 (bs, IH), 6.78 (m, 3H), 7.20 (t, J = 8.0 Hz, IH), 7.83 (d, J = 5.4 Hz, IH), 12.00 (s, IH). MS: m/z = 406 (MH+). Kinase: 0.15 µM.
4-chloro-N-[(5-methyl-1,2-oxazol-3-yl)methyl]pyrimidin-2-amine, used as starting material, was prepared as follows:

2-[(5-methyl-1,2-oxazol-3-yl)methylamino]pyrimidin-4-ol (3.67g, 17.8mmol, leq) and N-ethyl-N-propan-2-yl-propan-2-amine (4.02mL, 23.14mmol, 1.3eq) were stirred in toluene (20mL) and phosphorous oxychloride (2mL, 21.36mmol, 1.2eq) was added dropwise. The gummy suspension was heated at 80°C for 2h. The reaction was allowed to cool to room temperature and then poured into saturated sodium bicarbonate solution. The product was extracted with ethyl acetate (x2), washed with brine, dried (MgSO₄), filtered and evaporated. The crude product was purified on by silica column chromatography, eluting with 50% ethyl acetate in iso-hexane to give product as a white solid (1.87g, 47%).

IHNMR (CDCl3 400.13MHz) δ 2.39 (3H, s), 4.16 (2H, d), 5.78 (IH, s), 5.95 (IH, s), 6.63 (IH, d), 8.18 (IH, d). MS. m/z 225 (MH+).

2-[(3-methyl-1,2-oxazol-5-yl)methylamino]pyrimidin-4-ol, used as starting material, was prepared as follows:

(5-Methyl-1,2-oxazol-3-yl)methanamine (3.3g, 29.4mmol, 1.2eq) and 2-methylsulfonylpyrimidin-4-ol (3.48g, 24.5mmol, leq) were heated together at 160°C for 6h. The mixture was allowed to cool to room temperature and DCM was added. The suspension was stirred overnight and the product collected by filtration to give pale yellow solid (3.67g 73%).

IHNMR (DMSO) δ 2.35 (3H, s), 4.47 (2H, s), 5.58 (IH, d), 6.14 (IH, s), 6.95 (IH, s), 7.58 (IH, d), 10.9 (IH, s). MS. m/z 207 (MH+).

2-Methylsulfonylpyrimidin-4-ol used as starting material was prepared as follows:

2-Thiouracil (84g, 0.66mol, leq) was dissolved in aqueous sodium hydroxide (26g, 0.68mol, 1.05eq in 80mL water). The solution was diluted with MeOH (160mL). Iodomethane (47mL, 0.75mol, 1.15eq) was added dropwise. The temperature was kept between 35-40°C. A precipitate formed and the mixture was heated at 40°C for 1h. The mixture was stirred at
room temperature overnight, filtered and the solid was washed with water, methanol and dried at 45^\circ\text{C} in a vacuum oven to give 2-methylsulfanylpyrimidin-4-ol (53g, 57%).

\text{I}H \text{NMR (DMSO 400.13MHz)} \delta 2.37 (3H, s), 5.97 (IH, d), 7.74 (IH, d)

5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-amine used as starting material was prepared as follows:-

To 5-(3-methoxyphenyl)-3-oxo-pentanenitrile (5.37g, 26.42mmol, leq) in ethanol (80ml) was added hydrazine hydrate (1.41ml, 29.06mmol, l.leq). The reaction was refluxed for 3.5 h and then allowed to cool. The mixture was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and the organic layer was washed with water, brine, dried with magnesium sulphate, filtered and evaporated to yield a yellow oil (which solidified on standing). This was acidified and purified by SCX-3 column chromatography. The compound was eluted with 10% ammonia in methanol. After evaporation 5-[2-(3-methoxyphenyl)ethyl]-2H-pyrazol-3-amine was obtained (5.48g, 96% yield).

\text{1}H \text{NMR (300.132 MHz, DMSO)}: \delta 2.64 - 2.87 (4H, m), 3.73 (3H, s), 4.40 (IH, s), 5.19 (IH, s), 6.71 - 6.82 (3H, m), 7.18 (IH, t), 11.07 (IH, s). MS; m/z 218 (MH+)

5-(3-methoxyphenyl)-3-oxo-pentanenitrile used as starting material was prepared as follows:-

Acetonitrile (3.36ml, 64.25mmol, leq) was added to a slurry of sodium hydride (2.57g dispersion in mineral oil, 64.25mmol, leq) in anhydrous 1,4-dioxane (50ml) and the mixture was stirred at room temperature for 20 mins. Methyl 3-(3-methoxyphenyl)propanoate (10.4g, 53.54mmol, leq) in 1,4-dioxane (25ml) was added and the reaction was refluxed for 2h. The reaction mixture was cooled and quenched with water. The residue was dissolved in 2M HCl and extracted into ethyl acetate. The organic layer was separated, washed with 2M HCl, water and brine and dried over magnesium sulphate. Evaporation under reduced pressure gave yield to a yellow oil, which was purified by silica column chromatography, eluting with a mixture of 0-50% ethyl acetate in hexanes. Fractions containing the product were combined and evaporated to leave 5-(3-methoxyphenyl)-3-oxo-pentanenitrile (5.37g, 49% yield).

\text{1}H \text{NMR (300.132 MHz, CDC13)} \delta 2.86 (4H, s), 3.32 (2H, s), 3.73 (3H, s), 6.64 - 6.72 (3H, m), 7.14 (IH, t)
Example 3

N-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-N-[(5-methyl-1,2-oxazol-3-yl)methyl]pyrimidine-2,4-diamine

4-chloro-N-[(5-methyl-1,2-oxazol-3-yl)methyl]pyrimidin-2-amine (120mg, 0.534 mmol, 1.0 eq) was dissolved in ethanol (5 ml), 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine (132 mg, 0.534 mmol, 1.0 eq) was added and the mixture was stirred at 80 °C for 24 h. The reaction mixture was cooled to room temperature and the precipitate collected by filtration. The precipitate was dissolved in water (10 ml) and a drop of concentrated ammonia solution was added. The precipitate was collected by filtration, washed with water and dried in vacuo to yield N'-[5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-N-[(5-methyl-1,2-oxazol-3-yl)methyl]pyrimidine-2,4-diamine (172 mg, 74 %) as a white solid.

1H NMR (399.902 MHz, DMSO) δ 2.34 (s, 3H), 2.84 (s, 4H), 3.72 (s, 6H), 4.46 (d, J = 6.2 Hz, 2H), 6.11 (s, IH), 6.29 (s, 2H), 6.33 (t, J = 2.0 Hz, IH), 6.41 (d, J = 2.0 Hz, 2H), 7.09 (s, IH), 7.82 (d, J = 5.5 Hz, IH), 9.33 (s, IH), 11.89 (s, IH). MS: m/z = 436 (MH+). Kinase: 0.11 µM.

5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine, used as starting material was prepared as follows:

Acetonitrile (2.29ml, 43.61mmol, 1.2eq) was added to a slurry of sodium hydride (1.75g dispersion in mineral oil, 43.61mmol, 1.2eq) in anhydrous toluene (70ml) and the mixture stirred at room temperature for 30 mins. Ethyl 3-(3,5-dimethoxyphenyl)propanoate (8.66g, 36.34mmol, leq) in toluene (60ml) was added and the reaction was refluxed for 18h. After cooling, the reaction mixture was quenched with water and the solvent was evaporated under reduced pressure. The residue was dissolved in 2M HCl (50ml). The acidic solution was extracted with ethyl acetate. The organic extracts were combined and washed with water, brine and dried over magnesium sulphate. After filtering, the solvent was evaporated under reduced pressure to yield the crude product as a yellow oil. The oil was purified by silica column chromatography (eluting with DCM) and the desired fractions were combined and evaporated to yield a cream solid (3.76g, 44% yield). To the cream solid (3.72g, 15.96mmol, leq) in ethanol (55ml) was added hydrazine hydrate (852μl, 17.56mmol, 1.1eq). The reaction was refluxed for 24h and then cooled to room temperature. After evaporation under reduced pressure, the residue was extracted into DCM. The organic layers were washed with water,
brine, dried with magnesium sulphate, filtered and evaporated under reduced pressure to afford 5-[2-(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-amine as a pale yellow solid (3.76g, 42% over 2 steps).

1H NMR (300.132 MHz, DMSO) δ 2.64 - 2.82 (4H, m), 3.71 (6H, s), 4.07 - 4.72 (2H, m), 5.20 (IH, s), 6.31 (IH, t), 6.38 (2H, d). MS: m/z 248 (MH+).

Example 4
N'-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyr azol-3-yl]-N-[(5-methyl-1,2-oxazol-3-yl)methyl]pyrimidine-2,4-diamine

4-chloro-N-[(5-methyl-1,2-oxazol-3-yl)methyl]pyrimidin-2-amine (120mg, 0.534 mmol, 1.0 eq) was dissolved in ethanol (5 ml), 5-[3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine (133 mg, 0.534 mmol, 1.0 eq) was added and the mixture was stirred at 80 °C for 48 h. The solvent was evaporated and the residue purified on reverse-phase basic prep. HPLC using a 30-40% gradient of acetonitrile in water containing 1% ammonium hydroxide solution. The clean fractions were taken and evaporated to yield N'-[5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-yl]-N-[(5-methyl-1,2-oxazol-3-yl)methyl]pyrimidine-2,4-diamine (21 mg, 9%) as a colourless gum.

1H NMR (399.902 MHz, DMSO) δ 2.37 (s, 3H), 3.75 (s, 6H), 4.48 (d, J = 5.5 Hz, 2H), 5.07 (s, 2H), 5.29 (bs, IH), 6.01 (d, J = 5.5 Hz, IH), 6.15 (s, IH), 6.44 (s, IH), 6.60 (d, J = 1.9 Hz, 2H), 7.63 (bs, IH), 7.93 (d, J = 5.4 Hz, IH), 9.99 (bs, IH), 11.93 (bs, IH). MS: m/z = 438 (MH+). Kinase: 0.01 μM.

5-[(3,5-dimethoxyphenyl)methoxy]-2H-pyrazol-3-amine was prepared as in Example 3.

Example 5
3-[[2-[(3,5-dimethyl-1,2-oxazol-3-yl)methylamino] pyrimidin-4-yl] amino]-1H-pyrazol-3-yl]ethyl] phenol

N'-[5-[(3,5-dimethoxyphenyl)ethyl]-2H-pyrazol-3-yl]-N-[(5-methyl-1,2-oxazol-3-yl)methyl]pyrimidine-2,4-diamine (150 mg, 0.370 mmol, 1.0 eq) was dissolved in DCM (10 ml) under nitrogen and cooled to 0 °C. Boron tribromide 1M solution in DCM (1.85 mmol, 1.85 ml, 5.0 eq) was added dropwise and the reaction mixture was stirred for 3 h, during which time it was allowed to warm slowly to room temperature. The reaction mixture was
cooled with ice and methanol (5 ml) was added dropwise. The mixture was evaporated and the residue dissolved in DCM and purified on by silica column chromatography, eluting with a gradient of 4 - 10% MeOH in DCM. The clean fractions were combined, evaporated and dried in vacuo to yield 3-[2-[5-[[2-(5-methyl-1,2-oxazol-3-yl)methylamino]pyrimidin-4-yl]amino]-IH-pyrazol-3-yl]ethyl]phenol (88 mg, 61%) as an orange solid.

\[ \text{MS: } m/z = 392 (MH^+) \]

Kinase: 0.07 µM.

**Example 6**

N’-[5-[[3-(methoxyphenyl)ethyl]-2H-pyrazol-3-yl]-N-[[5-(methyl-1,2-oxazol-3-yl)methyl]pyrimidine-2,4-diamine was prepared as in Example 2.

**Example 15**

N’-[5-[[3-fluorophenyl]methoxy]-2H-pyrazol-3-yl]-N-[[5-(methyl-1,2-oxazol-3-yl)methyl]pyrimidine-2,4-diamine

4-chloro-N-[[5-(methyl-1,2-oxazol-3-yl)methyl]pyrimidin-2-amine (120 mg, 0.534 mmol, 1.0 eq) was dissolved in ethanol (5 ml), 5-[[3-fluorophenyl]methoxy]-IH-pyrazol-3-amine (111 mg, 0.534 mmol, 1.0 eq) was added and the mixture was stirred at 80 °C for 28 h. The solvent was evaporated and the residue purified on reverse-phase basic prep. HPLC using a 31-41% gradient of acetonitrile in water containing 1% ammonium hydroxide solution. The clean fractions were taken and evaporated to yield N’-[5-[2-(3-fluorophenyl)ethyl]-2H-pyrazol-3-yl]-N-[[5-(methyl-1,2-oxazol-3-yl)methyl]pyrimidine-2,4-diamine (80 mg, 38%) as a colourless solid.

\[ \text{MS: } m/z = 396 (MH^+) \]

Kinase: 0.36 µM.

5-[[3-fluorophenyl]methoxy]-IH-pyrazol-3-amine, used as starting material, was prepared as follows:
3-Amino-5-hydroxypyrazole (2.16g, 21.82mmol, leq) and triphenylphosphine (6.88g, 26.2mmol, 1.2eq) were stirred in DCM (22ml) for 30 mins. After this time, diisopropyl azodicarboxylate (5.16ml, 26.2mmol, 1.2eq) was slowly added, keeping the temp below 20 °C with a water bath, and the resulting mixture stirred for a further 45 mins. A solution of (3-fluorophenyl)methanol (3.3g, 26.2mmol) in DCM (10ml) was added slowly and the reaction left to stir at room temperature for 24 h. After this time the solid was filtered off and the solution extracted with 2M HCl solution (3x30ml). The aqueous layer was washed with diethyl ether (2x30ml) and then basified to pH 9 using ammonium hydroxide (with cooling). The solution was extracted with DCM (3x30ml) and the organic fractions combined, dried over magnesium sulphate and concentrated to give 5-[(3-fluorophenyl)methoxy]-1H-pyrazol-3-amine as a white solid (428mg, 10%).

IH NMR (300.132 MHz, DMSO) δ 4.76 (s, IH), 4.93 (s, 2H), 5.06 (s, 2H), 7.09 - 7.15 (m, IH), 7.18 - 7.24 (m, 2H), 7.37 - 7.44 (m, IH), 10.41 (s, IH). MS: m/z 208 (MH+)

**Kinase assay (using Caliper technology)**

To determine inhibition of FGFR activity, kinase assays were conducted using Caliper technology.

Kinase activity assays were performed in Greiner 384-well low volume plates, with a total reaction volume of 12ul per well. Final concentration of FGFR1 active kinase in each reaction well was 7.2nM. The substrate for each assay was a custom peptide with fluorescent tag (13 amino acids in length) the sequence of which was specific for FGFR1 kinase.

Compounds were serially diluted in 5% (v/v) DMSO, before being added to assay plates. The Enzyme (at 7.2nM [final]) and Substrate (at 3.6uM [final]) were added separately to the compound plates, in reaction buffer [comprising: 50mM MOPS - pH 6.5, 0.004% Triton, 2.4mM DTT, 12mM MgCl₂, 408uM ATP] resulting in a final DMSO concentration in the reaction mix of 0.8%.

Assay plates were incubated at room temperature for 1.5h, before the reaction was stopped with the addition of buffer [comprising: 100mM HEPES - pH7.5, 0.033% Brij-35, 0.22% Caliper Coating Reagent #3, 88mM EDTA, 5% DMSO]. Stopped assay plates were then read using the Caliper LabChip® LC3000 (which uses microfluidics to measure a shift in mobility between fluorescent labelled peptide and the FGFR1 kinase - phosphorylated form of this peptide).
The mean data values for each compound concentration, untreated control wells and 100% inhibition control wells were used to determine the IC50 for each test compound. The IC50 is the concentration of compound, which inhibits FGFR1 kinase activity by 50% in the context of this assay.


This assay is designed to detect inhibitors of transiently expressed FGFR1 phosphorylation by antibody staining of fixed cells detected using ArrayScan technology.

Cos-1 cells were routinely passaged in DMEM (Gibco BRL, 41966) plus 3% foetal calf serum (FCS), 1% L-glutamine (Gibco BRL, 25030) to a confluence of 80%. To undertake the assay, Cos-1 cells were harvested at 90-95% confluence for cell transfection. For each 96-well plate, 24ul Lipofectamine 2000 was added to 809ul OptiMEM and incubated at room temperature for 5 minutes. For each 96 well plate, 20ug 3' FLAG tagged FGFR1/pcDNA3.1 (In-house clone15, MSD 4793) was diluted with OptiMEM to a total volume of 833ul. Equal volumes of DNA and Lipofectamine 2000 were combined (DNA: Lipid = 1:1.2 ratio) and incubated at room temperature for 20 minutes.

The harvested Cos-1 cells are counted using a coulter counter and diluted further with 1% FCS/DMEM to 2.5 x 10⁵ cells/ml. For each 96-well, 8.33ml cells were required. The complexed transfection solution was added to the cell solution and the cells were seeded at 2.5x10⁵ cells/well in DMEM plus 1% foetal calf serum, 1% L-glutamine in 96 well plates (Costar, 3904) and incubated at 37°C (+5% CO₂) in a humidified incubator overnight (24hrs). The following day, the plates were dosed with 25 ul1 compound (diluted from 10 mM stock in DMSO using serum free DMEM) and the plates were returned to a humidified 37°C (+5% CO₂) incubator for one hour. Media was removed from the wells using vacuum aspiration; cells were fixed by adding 50ul of 100% methanol to each well and incubated at room temperature for 20 minutes. The fixative solution was then removed and the wells were washed once with 200ul phosphate buffered saline (PBS/A) before permeabilising the cells by the addition of 50ul/ well 0.1% triton/ PBS/A for 20 minutes at room temperature. The permeabilisation solution was then removed and the cells washed once more with 200ul / well PBS/A before the addition of 40ul 1/1000 primary antibody solution (Cell Signalling
Technologies #CS3476; mouse anti-phospho FGFRl diluted in PBS/A with 10% FCS + 0.1% Tween20) to each well.

Following incubation at room temperature for 1 hour, the antibody solution was removed and the wells were washed once with 200ul / well PBS/A. Then 40ul 1/500 secondary antibody (Al 1005; goat anti-mouse 594) solution and 1/10000 Hoechst (diluted together in PBS/A with 10% FCS + 0.1% Tween 20) were added and the plate incubated in the dark at room temperature for one hour. Finally, the plates were washed once with 200ul / well PBS/A, leaving the final wash in the wells before sealing the plates. The plates were read on an Arrayscan (Cellomics). The Channel 2 (594nm) values obtained from undosed (max) and reference compound (min) wells within a plate are used to set boundaries for 0% and 100% compound inhibition. Compound data is normalized against these values to determine the dilution range of a test compound that gives 50% inhibition of phosphorylated FGFRl.

Cell based inhibition of transiently expressed FGFRl IIIc phosphorylation via use of ECHO technology (measured using phospho-specific primary and fluorescent secondary antibodies).

This assay is designed to detect inhibitors of transiently expressed FGFRl phosphorylation by antibody staining of fixed cells detected using ArrayScan technology.

Cos-1 cells were routinely passaged in DMEM (Gibco BRL, 41966) plus 3% foetal calf serum (FCS), 1% L-glutamine (Gibco BRL, 25030) to a confluence of 80%. To undertake the assay, Cos-1 cells were harvested at 90-95% confluence for cell transfection.

For each 96-well plate, 24µl Lipofectamine 2000 was added to 809ul OptiMEM and incubated at room temperature for 5 minutes. For each 96 well plate, 20ug 3’ FLAG tagged FGFRl/ pcDNA3.1 (In-house clonel5, MSD 4793) was diluted with OptiMEM to a total volume of 833µl. Equal volumes of DNA and Lipofectamine 2000 were combined (DNA: Lipid = 1:1.2 ratio) and incubated at room temperature for 20 minutes.

The harvested Cos-1 cells are counted using a coulter counter and diluted further with 1% FCS/DMEM to 2.5 x 10^5 cells/ml. For each 96-well, 8.33ml cells were required. The complexed transfection solution was added to the cell solution and the cells were seeded at 2.5x10^5 cells/ well in DMEM plus 1% foetal calf serum, 1% L-glutamine in 96 well plates (Costar, 3904) and incubated at 37°C (+5% CO₂) in a humidified incubator overnight (24hrs). The following day, compounds from dry weight samples were dissolved in 100% DMSO to give 10mM concentration. 40µl of the compound was dispensed into the wells of each
quadrant across the 384 Labcyte plate (inclusive of a positive control (100% DMSO), a negative control (10µM) and a reference compound (25OnM)). The 384 Labcyte plate was then transferred to the Hydra to dilute the compounds 1:100 into the remaining wells of the quadrant. 70µl of media was aspirated from the assay plate using the Quadra before the plate was transferred onto the ECHO 550. The 384 Labcyte compound plate was also transferred onto the ECHO 550. Compound transfer to the assay plate on the ECHO 550 was at concentration ranges 1) 10 µM, 2) 3 µM, 3) 1µM, 4) 0.3µM, 5) 0.1µM, 6) 0.01.

The plates were gently tapped to mix compound in with the cell media and left to incubate at 37°C with 5% CO₂ for 1 hour. Media was removed from the wells using vacuum aspiration; cells were fixed by adding 50µl of 100% methanol to each well and incubated at room temperature for 20 minutes. The fixative solution was then removed and the wells were washed once with 200µl phosphate buffered saline (PBS/A) before permeabilising the cells by the addition of 50ul/ well 0.1% triton/ PBS/A for 20 minutes at room temperature. The permeabilisation solution was then removed and the cells washed once more with 200µl / well PBS/A before the addition of 40µl 1/1000 primary antibody solution (Cell Signalling Technologies #CS3476; mouse anti-phospho FGFR1 diluted in PBS/A with 10% FCS + 0.1% Tween20) to each well. Following incubation at room temperature for 1 hour, the antibody solution was removed and the wells were washed once with 200ul / well PBS/A. Then 40µl 1/500 secondary antibody (Al 1005; goat anti-mouse 594) solution and 1/10000 Hoechst (diluted together in PBS/A with 10% FCS + 0.1% Tween 20) were added and the plate incubated in the dark at room temperature for one hour. Finally, the plates were washed once with 200µl / well PBS/A, leaving the final wash in the wells before sealing the plates. The plates were read on an Arrayscan (Cellomics). The Channel 2 (594nm) values obtained from undosed (max) and reference compound (min) wells within a plate are used to set boundaries for 0% and 100% compound inhibition. Compound data was normalized against these values to determine the dilution range of a test compound that gives 50% inhibition of phosphorylated FGFR1.
1. A compound of formula (I):

\[
\begin{align*}
R^1 & \quad \text{a } \text{Ci-C}_6\text{alkyl optionally substituted by one or more } R^{13}, \\
& \quad \text{a } \text{C}_3\text{-C}_5\text{cycloalkyl optionally substituted by one or more } R^{14}, \\
& \quad \text{a } \text{C}_2\text{-C}_6\text{alkenyl optionally substituted by one or more } R^{15}, \\
& \quad \text{a } \text{4- to 6-membered heterocyclyl group optionally substituted by one or more } R^{16}, \\
& \quad \text{a } \text{Ci-C}_6\text{alkoxy group optionally substituted by one or more } R^{17}, \\
& \quad \text{a } \text{C3-Ci2carbocyclyloxy group optionally substituted by one or more } R^{18}, \\
& \quad \text{a } \text{5- to 6-membered heterocyclyloxy group optionally substituted by one or more } R^{19}, \\
& \quad \text{a } -\text{S(O)}_x\text{R}^{5} \text{ group,} \\
& \quad \text{a } -\text{S(O)}_2\text{NR}^{6}\text{R}^{7} \text{ group, or} \\
\end{align*}
\]

\[\text{A-B;}\]

\[\text{R}^{2} \text{ represents hydrogen or}\]

\[\text{a } \text{Ci-C}_3\text{alkyl group optionally substituted by one or more substituents}\]

\[\text{selected from } \text{Ci-C}_3\text{alkoxy, cyano, hydroxyl, amino (-NH}_2\text{),}\]

\[\text{mono-Ci-C}_3\text{alkyamino and di-(Ci-C}_3\text{alky)amino;}\]

\[\text{R}^{4} \text{ represents hydrogen,}\]

\[\text{a } \text{Ci-C}_6\text{alkyl group optionally substituted with d-C}_3\text{alkoxy, hydroxyl,}\]

\[\text{amino (-NH}_2\text{), mono-Ci-C}_3\text{alkyamino and di-(Ci-C}_3\text{alky)amino,}\]

\[\text{wherein}\]

\[\text{R}^{1} \text{ represents } \text{a } \text{Ci-C}_6\text{alkyl optionally substituted by one or more } R^{13}, \]

\[\text{a } \text{C}_3\text{-C}_5\text{cycloalkyl optionally substituted by one or more } R^{14}, \]

\[\text{a } \text{C}_2\text{-C}_6\text{alkenyl optionally substituted by one or more } R^{15}, \]

\[\text{a } \text{4- to 6-membered heterocyclyl group optionally substituted by one or more } R^{16}, \]

\[\text{a } \text{Ci-C}_6\text{alkoxy group optionally substituted by one or more } R^{17}, \]

\[\text{a } \text{C3-Ci2carbocyclyloxy group optionally substituted by one or more } R^{18}, \]

\[\text{a } \text{5- to 6-membered heterocyclyloxy group optionally substituted by one or more } R^{19}, \]

\[\text{a } -\text{S(O)}_x\text{R}^{5} \text{ group,} \]

\[\text{a } -\text{S(O)}_2\text{NR}^{6}\text{R}^{7} \text{ group, or} \]

\[\text{A-B;}\]
a C1-C6 alkyl group optionally substituted with C1-C3 alkoxy,
a C1-C6 alkenyl group optionally substituted with C1-C3 alkoxy,
a C3-C5 cycloalkyl group optionally substituted with C1-C3 alkoxy,
a C1-C6 alkoxy group optionally substituted with d-C3 alkoxy,
hydroxyl, amino (-NH2), mono-C1-C3 alky amino and
di-(C1-C3 alky) amino,
-C(O)NR8R9,
-NR10R11,
-S(O)yR12;

A represents a C2-alkylene optionally substituted by one or more R20,
a C1-alkyleneoxy optionally substituted by one or more R21, or
a oxyC1-alkylene optionally substituted by one or more R22;
B represents a 5- or 6-membered aromatic ring optionally comprising at least one
ring heteroatom selected from nitrogen, oxygen and sulphur, the
aromatic ring being optionally substituted by one or more R23 and
optionally wherein two or more adjacent R23 together with the atoms to
which they are attached form a partially or fully unsaturated 4- to 6-
membered ring;

R5 represents a C1-C6 alkyl, C3-C6 cycloalkyl or -CH2Ar wherein Ar represents a 5- or
6-membered aromatic ring optionally comprising at least one ring
heteroatom selected from nitrogen, oxygen and sulphur, the aromatic
ring being optionally substituted by one or more R24 and optionally
wherein two or more adjacent R24 together with the atoms to which
they are attached form a partially or fully unsaturated 4- to 6-membered
ring;

R6 and R7 each independently represent hydrogen, d-C4 alkyl or C3-C6 cycloalkyl, or
R6 and R7 together with the nitrogen atom to which they are attached form a 4- to
6-membered saturated heterocycle optionally comprising an additional heteroatom
selected from oxygen, sulphur or nitrogen wherein each R6 and R7 independently may
be optionally substituted on carbon by one or more substituents R25 and wherein if
said heterocycle contains an -NH- moiety that nitrogen may be optionally substited by
a group selected from R26;
R^8 and R^9 each independently represent hydrogen, Ci-C_4 alkyl or C_3-Cecycloalkyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle optionally comprising an additional heteratom selected from oxygen, sulphur or nitrogen wherein each R^8 and R^9 independently may be optionally substituted on carbon by one or more substituents R^{27} and wherein if said heterocycle contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{28};

R^{10} and R^{11} each independently represent hydrogen, Ci-C_4 alkyl or C_3-Cecycloalkyl, or R^{10} and R^{11} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle optionally comprising an additional heteratom selected from oxygen, sulphur or nitrogen wherein each R^{10} and R^{11} independently may be optionally substituted on carbon by one or more substituents R^{29} and wherein if said heterocycle contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{30};

R^{12} represents Ci-C_6 alkyl or C_3-Cecycloalkyl;

R^{13}, R^{14}, R^{15}, R^{20}, R^{21}, R^{22}, R^{36} and R^{38} each independently is -NR^{22}R^{33}, -C(O)NR^{34}R^{35}, cyano, hydroxyl or a group selected from Ci-C_6 alkyl, Ci-C_6 alkoxy, C_3-C_6 cycloalkyl, Ci-C_6 alkylthio wherein said group may be optionally substituted by one or more R^{31};

R^{16} and R^{17} each independently is selected from R^{36} and a 5- or 6-membered aromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, wherein the aromatic ring is optionally substituted by one or more substituents selected from R^{37};

R^{18}, R^{19}, R^{37} and R^{42} each independently is R^{38}, -SO_2NR^{39}R^{40}, nitro, carboxyl or a group selected from a C_2-Calkenyl, Ci-C_6 alkoxy carbonyl, Ci-C_6 alkyl carbonyl, Ci-Calkyl carbonylamino, phenyl carbonyl, -S(0)_{m}Ci-C_6 alkyl wherein said group may be optionally substituted by one or more R^{41};

R^{23} and R^{24} each independently is R^{42}, -OS(O)_{2}Ci-C_6 alkyl or a group selected from phenyl, benzyl, benzyl oxo wherein said group may be optionally substituted by one or more R^{43};
R\textsuperscript{25}, R\textsuperscript{27}, R\textsuperscript{29}, R\textsuperscript{31}, R\textsuperscript{41}, R\textsuperscript{43}, R\textsuperscript{46} and R\textsuperscript{48} each independently is selected from halogen, d-C\textsubscript{6}\textsuperscript{3}alkyl, d-C\textsubscript{6}alkoxy, Ci-C\textsubscript{6}alkylthio, amino (-NH\textsubscript{2}), mono- and di-
Ci-C\textsubscript{6}alkyamino, cyano, hydroxyl and trifluoromethyl;
R\textsuperscript{26}, R\textsuperscript{28}, R\textsuperscript{30}, R\textsuperscript{45}, R\textsuperscript{47} and R\textsuperscript{49} each independently is selected from Ci-C\textsubscript{6}alkyl, benzyl, Ci-C\textsubscript{6}alkoxycarbonyl, Ci-C\textsubscript{6}alkylcarbonyl, phenylcarbonyl, Ci-C\textsubscript{6}alkylsulphonyl and phenylsulphonyl;
5
R\textsuperscript{32} and R\textsuperscript{33} each independently represent hydrogen, Ci-C\textsubscript{4}alkyl or C\textsubscript{3}-Cycloalkyl, or
R\textsuperscript{32} and R\textsuperscript{33} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle optionally comprising an additional heteratom selected from oxygen, sulphur or nitrogen wherein each R\textsuperscript{32} and R\textsuperscript{33} independently may be optionally substituted on carbon by one or more substituents R\textsuperscript{44} and wherein if said heterocycle contains an -NH- moiety that nitrogen may be optionally substited by a group selected from R\textsuperscript{45};
10
R\textsuperscript{34} and R\textsuperscript{35} each independently represent hydrogen, Ci-C\textsubscript{4}alkyl or C\textsubscript{3}-Cycloalkyl, or
R\textsuperscript{34} and R\textsuperscript{35} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle optionally comprising an additional heteratom selected from oxygen, sulphur or nitrogen wherein each R\textsuperscript{34} and R\textsuperscript{35} independently may be optionally substituted on carbon by one or more R\textsuperscript{46} and wherein if said heterocycle contains an -NH- moiety that nitrogen may be optionally substited by a group selected from R\textsuperscript{47};
15
R\textsuperscript{39} and R\textsuperscript{40} each independently represent hydrogen, Ci-C\textsubscript{4}alkyl or C\textsubscript{3}-Cycloalkyl, or
R\textsuperscript{39} and R\textsuperscript{40} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle optionally comprising an additional heteratom selected from oxygen, sulphur or nitrogen wherein each R\textsuperscript{39} and R\textsuperscript{40} independently may be optionally substituted on carbon by one or more R\textsuperscript{48} and wherein if said heterocycle contains an -NH- moiety that nitrogen may be optionally substited by a group selected from R\textsuperscript{49};
20
m is 0, 1 or 2;
x is 0, 1 or 2;
y is 0, 1 or 2; and
25
wherein
(i) when \( R^1 \) is an optionally substituted \( C_2\text{-}C_6 \)alkenyl, \( 4\text{-}6 \)membered heterocyclyl group, \( C_4\text{-}C_6 \)alkoxy group, \( C_3\text{-}C_6 \)carbocyclyloxy, \( 5\text{-}6 \)membered heterocyclyloxy, -\( \text{SO}_x \)R\(^5\), -\( \text{SO}_x \)NR\(^6\)R\(^7\) or -A-B group,

\[ R^3 \text{ represents a } C_i\text{-}C_s \text{alkyl group optionally substituted by one or more substituents selected from } C_i\text{-}C_3 \text{alkoxy, cyano, hydroxyl, amino (-NH}_2\text{), mono-Ci-C_s \text{alkylamino and di-(Ci-C_3 \text{alkyl)amino,}} \]

\[ \text{a } C_3\text{-}C_5 \text{cycloalkyl group optionally substituted by one or more substituents selected from Ci-C_3alkyl and Ci-C_3alkoxy,} \]

\[ \text{a } 3\text{-}5 \text{membered saturated heterocyclyl group optionally substituted with by one or more substituents selected from Ci-C_3alkyl, Ci-C_3alkoxy and C_3Cycloalkyl,} \]

\[ \text{a } 5\text{-}6 \text{membered aromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur,} \]

\[ \text{a mono-Ci-C}_3 \text{alkylaminocarbonyl group,} \]

\[ \text{a di-(Ci-C}_3 \text{alkyl)aminocarbonyl group,} \]

\[ \text{a Ci-C_3alkoxy carbonyl group,} \]

\[ \text{a } \text{CONH}_2 \text{ group,} \]

\[ \text{a } \text{CO}_2 \text{H group;} \]

or (ii) when \( R^1 \) is an optionally substituted \( C_6 \)alkyl or a \( C_3\text{-}C_5 \)cycloalkyl group,

\[ R^3 \text{ represents a } C_i\text{-}C_s \text{alkyl group optionally substituted by one or more substituents selected from Ci-C_3alkoxy, cyano, hydroxyl, amino (-NH}_2\text{), mono-Ci-C}_3 \text{alkylamino and di-(Ci-C}_3 \text{alkyl)amino,} \]

\[ \text{a } C_3\text{-}C_5 \text{cycloalkyl group optionally substituted with Ci-C_3alkoxy,} \]

\[ \text{a } 3\text{-}5 \text{membered saturated heterocyclyl group optionally substituted with by one or more substituents selected from Ci-C_3alkyl, Ci-C_3alkoxy and C_3Cycloalkyl,} \]

\[ \text{a } \text{CONH}_2 \text{ group,} \]

\[ \text{a } \text{CO}_2 \text{H group;} \]

or a pharmaceutically acceptable salt thereof.

2. A compound or a pharmaceutically acceptable salt thereof according to Claim 1 wherein \( R^1 \) represents
a Ci-C₃ alkyl group substituted by one or more substituents selected from hydroxyl and Ci-C₃ alkoxy which may be optionally substituted by one or more substituents selected from halogen, Ci-C₃ alkyl and Ci-C₃ alkoxy,
a Ci-C₃ alkoxy group optionally substituted by one or more substituents selected from Ci-C₃ alkoxy and cyclopropyl,
a phenoxy group optionally substituted by one or more substituents selected from Ci-C₃ alkyl, Ci-C₃ alkoxy and cyclopropyl, or
-A-B wherein A represents a C2-alkylene or oxyCi-alkylene, and B represents a phenyl or pyridin-4yl ring wherein the phenyl or the pyridin-4yl ring may be optionally substituted by one or more R²³.

3. A compound or a pharmaceutically acceptable salt thereof according to Claim 2 wherein R¹ represents a 2-(3-methoxyphenyl)ethyl, 2-(3,5-dimethoxyphenyl)ethyl, 2-propoxy, (3,5-dimethoxyphenyl)methoxy, 2-(3-hydroxyphenyl)ethyl, or (3-fluorophenyl)methoxy group.

4. A compound or a pharmaceutically acceptable salt thereof according to any one of Claims 1 to 3 wherein R² represents hydrogen or a Ci-C₃ alkyl group.

5. A compound or a pharmaceutically acceptable salt thereof according to Claim 4 wherein R² represents hydrogen or methyl.

6. A compound or a pharmaceutically acceptable salt thereof according to Claim 5 wherein R² represents hydrogen.

7. A compound or a pharmaceutically acceptable salt thereof according to any one of Claims 1 to 6 wherein R³ represents a Ci-Cs alkyl group; or a C₃-Cscycloalkyl group.

8. A compound or a pharmaceutically acceptable salt thereof according to Claim 7 wherein R³ represents methyl, ethyl, propyl, /-propyl or cyclopropyl.
9. A compound or a pharmaceutically acceptable salt thereof according to Claim 8 wherein \( R^3 \) represents methyl, or cyclopropyl.

10. A compound or a pharmaceutically acceptable salt thereof according to any one of Claims 1 to 9 wherein \( R^4 \) hydrogen, a \( \text{Ci-C}_6 \text{alkyl} \) group; a \( \text{C}_3 \text{-Cycloalkyl} \); a \( \text{Ci-C}_6 \text{alkoxy} \) group.

11. A compound or a pharmaceutically acceptable salt thereof according to Claim 10 wherein \( R^4 \) represents hydrogen, methyl or methoxy.

12. A compound or a pharmaceutically acceptable salt thereof according to Claim 11 wherein \( R^4 \) represents hydrogen.

13. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of Claims 1 to 12, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

14. A process for the preparation of a pharmaceutical composition as claimed in Claim 16 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 12, with a pharmaceutically acceptable adjuvant, diluent or carrier.

15. A compound of formula (I), or a pharmaceutically-acceptable salt thereof, as claimed in any one of Claims 1 to 12 for use in therapy.

16. Use of a compound of formula (I), or a pharmaceutically acceptable salt, as claimed in any one of claims 1 to 12 in the manufacture of a medicament for use in therapy.

17. A method of treating cancer which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of Claims 1 to 12.
18. A method of modulating FGFR activity which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of Claims 1 to 12.
**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Relevant to claim No</th>
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<td>X</td>
<td>WO 03/048133 A (ASTRAZENECA AB [SE]); BARLAAM BERNARD [FR]; PAPE ANDREW [GB]; THOMAS AM) 12 June 2003 (2003-06-12) the whole document, in particular example 56 and claim 1</td>
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**D. Further documents are listed in the continuation of Box C**

- " 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
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**Date of the actual completion of the international search:** 15 October 2008

**Date of mailing of the international search report:** 22/10/2008

**Name and mailing address of the ISA/ European Patent Office P B 5818 Palenlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040 Fax (+31-70) 340-3016**

Authorized officer: Mates Valdi viel so, J
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