4-(PYRID-2-YL)AMINO SUBSTITUTED PYRAMIDINE AS PROTEIN KINASE INHIBITORS

The invention concerns certain novel pyrimidine derivatives, or pharmaceutically-acceptable salts thereof, which possess anti-tumour activity and are accordingly useful in methods of treatment of the human or animal body. The invention also concerns processes for the manufacture of the pyrimidine derivatives, to pharmaceutical compositions containing them and to their use in therapeutic methods, for example in the manufacture of medicaments for use in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

The insulin-like growth factor (IGF) axis consists of ligands, receptors, binding proteins and proteases. The two ligands, IGF-I and IGF-II, are mitogenic peptides that signal through interaction with the type 1 insulin-like growth factor receptor (IGF-1R), a hetero-tetrameric cell surface receptor. Binding of either ligand stimulates activation of a tyrosine kinase domain in the intracellular region of the β-chain and results in phosphorylation of several tyrosine residues resulting in the recruitment and activation of various signalling molecules. The intracellular domain has been shown to transmit signals for mitogenesis, survival, transformation, and differentiation in cells. The structure and function of the IGF-1R has been reviewed by Adams *et al* (*Cellular and Molecular Life Sciences*, **57**, 1050-1093, 2000). The IGF-IIR (also known as mannose 6-phosphate receptor) has no such kinase domain and does not signal mitogenesis but may act to regulate ligand availability at the cell surface, counteracting the effect of the IGF-1R. The IGF binding proteins (IGFBP) control availability of circulating IGF and release of IGF from these can be mediated by proteolytic cleavage. These other components of the IGF axis have been reviewed by Collett-Solberg and Cohen (*Endocrine*, **12**, 121-136, 2000).

There is considerable evidence linking IGF signalling with cellular transformation and the onset and progression of tumours. IGF has been identified as the major survival factor that protects from oncogene induced cell death (Harrington *et al, EMBO J*, **13**, 3286-3295, 1994). Cells lacking IGF-1R have been shown to be refractory to transformation by several different oncogenes (including SV40T antigen and ras) that efficiently transform corresponding wild-type cells (Sell *et al., Mol. Cell Biol.,* 14, 3604-12, 1994). Upregulation of components of the IGF axis has been described in various tumour cell lines and tissues, particularly tumours of the breast (Surmacz, *Journal of Mammary Gland Biology & Neoplasia*, **5**, 95-105, 2000), prostate (Djavan *et al, World J. Urol.*, **19**, 225-233, 2001, and O'Brien *et al, Urology*,

58, 1-7, 2001) and colon (Guo *et al, Gastroenterology,* **102**, 1101-1108, 1992). Conversely, IGF-IIR has been implicated as a tumour suppressor and is deleted in some cancers (DaCosta *et al, Journal of Mammary Gland Biology & Neoplasia*, 5, 85-94, 2000). There are a growing number of epidemiological studies linking increased circulating IGF (or increased ratio of IGF-1 to IGFBP3) with cancer risk (Yu and Rohan, *J. Natl. Cancer Inst.*, **92**, 1472-1489, 2000). Transgenic mouse models also implicate IGF signalling in the onset of tumour cell proliferation (Lamm and Christofori, *Cancer Res.* **58**, 801-807, 1998, Foster et al, *Cancer Metas. Rev.*, **17**, 317-324, 1998, and DiGiovanni *et al, Proc. Natl. Acad. Sci.*, **97**, 3455-3460, 2000).

Several *in vitro* and *in vivo* strategies have provided the proof of principal that inhibition of IGF-1R signalling reverses the transformed phenotype and inhibits tumour cell growth. These include neutralizing antibodies (Kalebic *et al Cancer Res.*, **54**, 5531-5534, 1994), antisense oligonucleotides (Resnicoff *et al, Cancer Res.*, **54**, 2218-2222, 1994), triple-helix forming oligonucleotides (Rinninsland *et al, Proc. Natl. Acad.* Sci., **94**, 5854-5859, 1997), antisense mRNA (Nakamura *et al, Cancer Res.*, **60**, 760-765, 2000) and dominant negative receptors (D'Ambrosio *et al., Cancer Res.*, **56**, 4013-4020, 1996). Antisense oligonucleotides have shown that inhibition of IGF-1R expression results in induction of apoptosis in cells *in vivo* (Resnicoff *et al, Cancer Res.*, **55**, 2463-2469, 1995) and have been taken into man (Resnicoff *et al, Proc. Amer. Assoc. Cancer Res.*, 40 Abs 4816, 1999). However, none of these approaches is particularly attractive for the treatment of major solid tumour disease.

Since increased IGF signalling is implicated in the growth and survival of tumour cells, and blocking IGF-1R function can reverse this, inhibition of the IGF-1R tyrosine kinase domain is an appropriate therapy by which to treat cancer. *In vitro* and *in vivo* studies with the use of dominant-negative IGF-1R variants support this. In particular, a point mutation in the ATP binding site which blocks receptor tyrosine kinase activity has proved effective in preventing tumour cell growth (Kulik *et al, Mol. Cell. Biol.*, **17**, 1595-1606, 1997). Several pieces of evidence imply that normal cells are less susceptible to apoptosis caused by inhibition of IGF signalling, indicating that a therapeutic margin is possible with such treatment (Baserga, *Trends Biotechnol.,* 14, 150-2, 1996).

There are few reports of selective IGF-1R tyrosine kinase inhibitors. Parrizas *et al.* described tyrphostins that had some efficacy *in vitro and in vivo* (Parrizas *et al., Endocrinology,* 138:1427-33 (1997)). These compounds were of modest potency and

selectivity over the insulin receptor. Telik Inc. have described heteroaryl-aryl ureas which have selectivity over insulin receptors but potency against tumour cells *in vitro* is still modest (Published PCT Patent Application No. WO 00/35455). Novartis have disclosed a pyrazolopyrimidine compound (known as NVP-AEW541), which is reported to inhibit IGF-1R tyrosine kinase (Garcia-Echeverria *et al., Cancer Cell*, 5:231-39 (2004)). Axelar have described podophyllotoxin derivatives as specific IGFR tyrosine kinase inhibitors (Vasilcanu *et al., Oncogene*, 23: 7854-62 (2004)) and Aventis have described cyclic urea derivatives and their use as IGF-1R tyrosine kinase inhibitors (WO 2004/070050).

Additionally, several anti-IGFR antibodies are reported to block receptor signalling and show inhibition of tumour growth in animal models (Cohen *et al., Clin. Canc. Res.*, 11: 2063-73 (2005); Burtrum *et al., Canc. Res.*, 63: 8912-21 (2003); Goetsch *et al., Int. J. Cancer*, 113: 316-28 (2005) and Maloney *et al., Canc. Res.*, 63: 5073-83 (2003)).

Pyrimidine derivatives substituted at the 2- and 4- positions by a substituted amino group having IGF-IR tyrosine kinase inhibitory activity are described in WO 03/048133. Compounds in which the nitrogen atom of the amino substituent forms part of a heterocyclic ring are not disclosed in WO 03/048133.

WO 02/50065 discloses that certain pyrazolyl-amino substituted pyrimidine derivatives have protein kinase inhibitory activity, especially as inhibitors of Aurora-2 and glycogen synthase kinase-3 (GSK-3), and are useful for treating diseases such as cancer, diabetes and Alzheimer's disease. The compounds disclosed in this document have a substituted amino substituent at the 2-position of the pyrimidine ring but again there is no disclosure of compounds in which the nitrogen atom of the amino substituent forms part of a heterocyclic ring.

WO 01/60816 discloses that certain substituted pyrimidine derivatives have protein kinase inhibitory activity. There is no disclosure in WO 01/60816 of pyrimidine derivatives having a pyridyl-amino substituent at the 4-position on the pyrimidine ring and a N-linked azetidine or pyrrolidine ring at the 2-position on the pyrimidine ring.

Pyrazolyl-amino substituted pyrimidine derivatives having Aurora-2 and glycogen synthase kinase-3 (GSK-3) inhibitory activity in which the 2-position of the pyrimidine ring is substituted by an N-linked heterocyclic ring are disclosed generically in WO 02/22601, WO 02/22602, WO 02/22603, WO 02/22604, WO 02/22605, WO 02/22606, WO 02/22607 and WO 02/22608. There is no disclosure in these documents of pyrimidine compounds that contain a pyridyl-amino substituent at the 4-position of the pyrimidine ring and/or an

azetidinyl or pyrrolidinyl substituent at the 2-position of the pyrimidine ring, which azetidinyl or pyrrolidinyl substituent is itself substituted by a substituted heteroaryl ring.

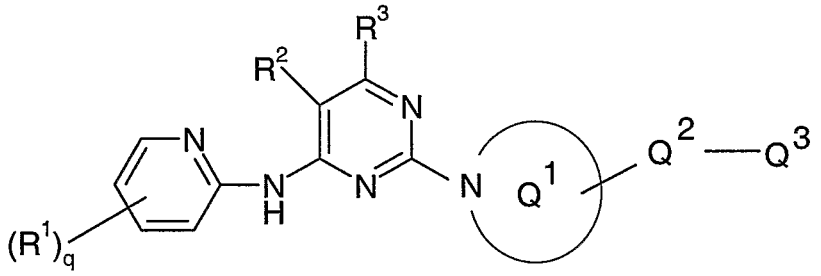
WO 2005/040159 (International patent application number PCT/GB2004/004307) discloses certain pyrimidine derivatives and their use in modulating insulin-like growth factor 1 receptor activity. There is no disclosure in this document of pyrimidine compounds that contain a pyridyl-amino substituent at the 4-position of the pyrimidine ring.

WO 2004/048365 discloses certain pyrimidine derivatives and their use as phosphotidylinositol (PI) 3-kinase inhibitors. There is no disclosure in this document of pyrimidine compounds that contain an azetidinyl or pyrrolidinyl substituent at the 2-position of the pyrimidine ring, which azetidinyl or pyrrolidinyl substituent is itself substituted by a substituted heteroaryl ring.

Substituted pyrimidine derivatives are also disclosed in WO 00/39101, WO 2004/056786 and WO 2004/080980, but none of these documents describe pyrimidine derivatives having a N-linked azetidinyl or pyrrolidinyl ring at the 2-position on the pyrimidine ring (especially where the azetidinyl or pyrrolidinyl substituent is itself substituted by a substituted heteroaryl ring).

We have now found that certain pyrimidine compounds that contain a pyridyl-amino substituent at the 4-position and a substituted azetidine or pyrrolidine ring at the 2-position on the pyrimidine ring possess potent anti-tumour activity. Without wishing to imply that the compounds disclosed in the present invention possess pharmacological activity only by virtue of an effect on a single biological process, it is believed that the compounds provide an anti-tumour effect by way of inhibition of IGF-1R tyrosine kinase activity.

According to a first aspect of the invention, there is provided a compound of formula (I):



(I)

wherein:

R^1 is selected from cyano, or from a (C1-C6)alkyl, amino, (C1-C4)alkylamino, di-[(C1-C4)alkyl]amino, carbamoyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl or

$-N(R^{1a})C(O)R^{1b}$ group, wherein R^{1a} and R^{1b} are each independently selected from hydrogen and (C1-C6)alkyl, each of which groups may be optionally substituted by one or more substituents independently selected from halogeno and (C1-C6)alkoxy;

q is 0, 1, 2 or 3;

$\mathbf{R^2}$ is selected from hydrogen, halogeno and trifluoromethyl;

$\mathbf{R^3}$ is selected from hydrogen, hydroxy and halogeno, or from a (C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl, (C1-C6)alkoxy, (C3-C8)cycloalkyl(C1-C6)alkoxy, (C1-C6)alkylcarbonyl, (C3-C8)cycloalkylcarbonyl, (C3-C8)cycloalkyl(C1-C6)alkylcarbonyl, (C1-C6)alkoxycarbonyl, amino, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, (C3-C8)cycloalkylamino, (C3-C8)cycloalkyl(C1-C6)alkylamino, (C1-C6)alkoxyamino, carbamoyl, (C1-C6)alkylcarbamoyl, di-[(C1-C6)alkyl]carbamoyl, $-C(O)R^{3b}$, $-OR^{3b}$, $-SR^{3b}$, $-NHR^{3b}$, $-N[(C1-C6)alkyl]R^{3b}$, $-S(O)_mR^{3a}$ or $-N(R^{3c})C(O)R^{3a}$ group, wherein m is 0, 1 or 2, R^{3a} is selected from a (C1-C6)alkyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl or (C1-C6)alkoxy group, R^{3b} is a saturated monocyclic 4-, 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur and R^{3c} is selected from hydrogen and (C1-C6)alkyl,

or R^3 is a saturated monocyclic 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur,

or R^3 is a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur,

or R^3 is a 2,7-diazaspiro[3.5]nonane group,

each of which groups or rings within R^3 may be optionally substituted by one or more substituents independently selected from (C1-C6)alkyl, (C1-C6)alkoxy, (C1-C6)alkoxy(C1-C6)alkyl, (C1-C6)alkoxy(C1-C6)alkoxy, halogen, hydroxy, trifluoromethyl, tri-[(C1-C4)alkyl]silyl, cyano, amino, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, (C3-C8)cycloalkylamino, (C3-C6)cycloalkyl(C1-C3)alkylamino, amino(C1-C6)alkyl, (C1-C6)alkylamino(C1-C6)alkyl, di-[(C1-C6)alkyl]amino(C1-C6)alkyl, (C3-C8)cycloalkylamino(C1-C6)alkyl, (C3-C6)cycloalkyl(C1-C3)alkylamino(C1-C6)alkyl, (C1-C6)alkoxycarbonyl, carbamoyl, (C1-C6)alkylcarbamoyl, di-[(C1-C6)alkyl]carbamoyl, (C1-C6)alkylthio, (C1-C6)alkylsulfonyl, (C1-C6)alkylsulfinyl, (C1-C6)alkanoyl, an alkanoylamino group $-N(R^{3d})C(O)R^{3e}$ wherein R^{3d} is selected from hydrogen and (C1-C6)alkyl and R^{3e} is selected from a (C1-C6)alkyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-

C6)alkyl or (C1-C6)alkoxy group, or a saturated monocyclic 3-, 4-, 5-, 6- or 7-membered ring, which ring may optionally comprise one or more heteroatoms selected from nitrogen, oxygen and sulfur, any of which substituents may be optionally substituted by one or more (C1-C4)alkyl, hydroxy or cyano groups;

-NQ^1 is a N-linked azetidinyl or pyrrolidinyl ring;

Q^2 is a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur, which ring is substituted by Q^3 and is optionally substituted, on any available ring atom, by one or more further substituents independently selected from (C1-C6)alkyl and (C1-C6)alkoxy (either of which (C1-C6)alkyl and (C1-C6)alkoxy substituent groups may be optionally substituted by one or more substituents independently selected from halogeno, amino, hydroxy and trifluoromethyl), halogeno, nitro, cyano, $-NR^4R^5$, carboxy, hydroxy, (C2-C6)alkenyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl, (C1-C4)alkoxycarbonyl, (C1-C4)alkylcarbonyl, (C2-C6)alkanoylamino, phenylcarbonyl, $-S(O)_p$(C1-C4)alkyl, $-C(O)NR^6R^7$ and $-SO_2NR^8R^9$, wherein R^4, R^5, R^6, R^7, R^8 and R^9 are each independently selected from hydrogen and (C1-C6)alkyl, or R^4 and R^5, or R^6 and R^7, or R^8 and R^9, when taken together with the nitrogen atom to which they are attached, may each independently form a saturated heterocyclic ring and p is 0, 1 or 2;

Q^3 is selected from a (C1-C6)alkyl, (C3-C6)cycloalkyl or (C3-C6)cycloalkyl(C1-C6)alkyl group or a saturated or unsaturated 5- or 6-membered monocyclic ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulfur, and wherein Q^3 is optionally substituted by one or more substituents independently selected from (C1-C6)alkyl and (C1-C6)alkoxy (either of which (C1-C6)alkyl and (C1-C6)alkoxy substituent groups may be optionally substituted by one or more substituents independently selected from halogeno, amino, hydroxy and trifluoromethyl), halogeno, nitro, cyano, $-NR^{10}R^{11}$, carboxy, hydroxy, (C2-C6)alkenyl, (C3-C8)cycloalkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C2-C6)alkanoylamino, phenylcarbonyl, $-S(O)_n$(C1-C6)alkyl, $-C(O)NR^{12}R^{13}$ and $-SO_2NR^{14}R^{15}$, wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are each independently selected from hydrogen and (C1-C6)alkyl, or R^{10} and R^{11}, or R^{12} and R^{13}, or R^{14} and R^{15}, when taken together with the nitrogen atom to which they are attached, may each independently form a saturated heterocyclic ring and n is 0, 1 or 2;

and wherein any saturated monocyclic ring optionally bears 1 or 2 oxo or thioxo substituents;

or a pharmaceutically-acceptable salt thereof.

In this specification, unless otherwise indicated, the term "alkyl" when used alone or in combination, includes both straight chain and branched chain alkyl groups, such as propyl, isopropyl and tert-butyl. However, references to individual alkyl groups such as "propyl" are specific for the straight-chain version only and references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only. A (C1-C6)alkyl group has from one to six carbon atoms including methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-pentyl, n-hexyl and the like. References to "(C1-C4)alkyl" will be understood accordingly to mean a straight or branched chain alkyl moiety having from one to four carbon atoms.

An analogous convention applies to other generic terms, for example, the terms "(C1-C6)alkoxy" and "(C1-C4)alkoxy", when used alone or in combination, will be understood to refer to straight or branched chain groups having from one to six, or from one to four, carbon atoms respectively and include such groups as methoxy, ethoxy, propoxy, isopropoxy and butoxy.

A "(C2-C6)alkenyl" group includes both straight chain and branched chain alkenyl groups having from two to six carbon atoms, such as vinyl, isopropenyl, allyl and but-2-enyl. Similarly, a "(C2-C6)alkynyl" group includes both straight chain and branched chain alkynyl groups having from two to six carbon atoms, such as ethynyl, 2-propynyl and but-2-ynyl.

The term "(C3-C8)cycloalkyl", when used alone or in combination, refers to a saturated alicyclic moiety having from three to eight carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. References to "(C3-C6)cycloalkyl" will be understood accordingly to mean a saturated alicyclic moiety having from three to six carbon atoms, representative examples of which are listed above.

As used herein, the term "halogeno" includes fluoro, chloro, bromo and iodo.

The term "optionally substituted" is used herein to indicate optional substitution by the group or groups specified at any suitable available position.

A "heteroatom" is a nitrogen, sulfur or oxygen atom. Where rings include nitrogen atoms, these may be substituted as necessary to fulfil the bonding requirements of nitrogen or they may be linked to the rest of the structure by way of the nitrogen atom. Nitrogen atoms may also be in the form of N-oxides. Sulfur atoms may be in the form of S, S(O) or SO_2.

Suitable values for the generic radicals referred to above include those set out below.

A suitable value for a substituent on R^3 when it is a "saturated monocyclic 3-, 4-, 5-, 6- or 7-membered ring, which ring may optionally comprise one or more heteroatoms selected from nitrogen, oxygen and sulfur" is a carbocyclic ring containing 3, 4, 5, 6 or 7 atoms (that is an alicyclic ring having ring carbon atoms only) or a heterocyclic ring containing 3, 4, 5, 6 or 7 atoms of which at least one is a heteroatom selected from nitrogen, oxygen and sulfur. When the "saturated monocyclic 3-, 4-, 5-, 6- or 7-membered ring, which ring may optionally comprise one or more heteroatoms selected from nitrogen, oxygen and sulfur" is a heterocyclic ring, the heterocyclic ring suitably contains from one to four (for example, from one to three, or one or two) heteroatoms independently selected from nitrogen, oxygen and sulfur. Unless specified otherwise, the heterocyclic ring may be carbon or nitrogen linked. Examples of suitable saturated monocyclic 3-, 4-, 5-, 6- or 7-membered carbocyclic rings include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Examples of suitable saturated monocyclic 3-, 4-, 5-, 6- or 7-membered heterocyclic rings include oxiranyl, azetidinyl, dioxanyl, trioxanyl, oxepanyl, dithianyl, trithianyl, oxathianyl, thiomorpholinyl, pyrrolidinyl, piperidinyl, imidazolidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and piperazinyl (particularly azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and piperazinyl). A saturated heterocyclic ring that bears 1 or 2 oxo or thioxo substituents may, for example, be 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidinyl, 2-thioxoimidazolidinyl, 2-oxopiperidinyl, 2,5-dioxopyrrolidinyl, 2,5-dioxoimidazolidinyl or 2,6-dioxopiperidinyl.

A suitable value for R^{3b} when it is a "saturated monocyclic 4-, 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur" is a heterocyclic ring containing four, five or six ring atoms, representative examples of which are listed above.

A suitable value for R^3 when it is a "saturated monocyclic 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur" is a heterocyclic ring containing five or six ring atoms, representative examples of which are listed above.

A suitable value for Q^2 or for R^3 when it is a "5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur" is a fully unsaturated, aromatic monocyclic ring containing five or six atoms of which at least one is a heteroatom selected from nitrogen, oxygen and sulfur, which ring may, unless otherwise specified, be carbon or nitrogen linked. Particularly, the 5- or 6-membered heteroaromatic

ring may contain from one to four (for example, from one to three, or one or two) heteroatoms independently selected from nitrogen, oxygen and sulfur. Examples of such heteroaromatic rings include pyridyl, imidazolyl, isoxazolyl, pyrazolyl, furyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl, thiazolyl, oxazolyl, oxadiazolyl, isothiazolyl, triazolyl, tetrazolyl and thienyl.

A suitable value for Q^3 when it is a "saturated or unsaturated 5- or 6-membered monocyclic ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulfur" is a saturated or fully or partially unsaturated monocyclic ring containing five or six atoms of which optionally at least one is a heteroatom selected from nitrogen, oxygen and sulfur, which ring may, unless otherwise specified, be carbon or nitrogen linked. The ring may have alicyclic or aromatic properties. An aromatic monocyclic ring may be aryl (such as phenyl) or heteroaromatic, representative examples of which are listed above.

When R^3 is a 2,7-diazaspiro[3.5]nonane group, it is preferably linked to the pyrimidine ring via. a nitrogen atom, particularly via. the nitrogen atom at the 7-position. When the 2,7-diazaspiro[3.5]nonane group carries a substituent, this may be at any available carbon or nitrogen atom, for example at any nitrogen atom that is not attached to the pyrimidine ring. A particular substituted 2,7-diazaspiro[3.5]nonane group may, for example, be 2-(tert-butoxycarbonyl)-2,7-diazaspiro[3.5]nonane.

Where R^4 and R^5, or R^6 and R^7, or R^8 and R^9, or R^{10} and R^{11}, or R^{12} and R^{13}, or R^{14} and R^{15} form a saturated heterocyclic ring, the only heteroatom present is the nitrogen atom to which R^4 and R^5, or R^6 and R^7, or R^8 and R^9, or R^{10} and R^{11}, or R^{12} and R^{13}, or R^{14} and R^{15} are attached. The saturated heterocyclic ring is preferably a 4-, 5-, 6- or 7-membered ring, including the nitrogen atom to which R^4 and R^5, or R^6 and R^7, or R^8 and R^9, or R^{10} and R^{11}, or R^{12} and R^{13}, or R^{14} and R^{15} are attached.

For the avoidance of any doubt, the nitrogen atom in the N-linked azetidine or pyrrolidine ring ($-NQ^1$) to which the pyrimidine group is attached is not quaternised; namely the pyrimidine group is attached to the nitrogen atom in the azetidine or pyrrolidine ring via. substitution of an NH group in the azetidine or pyrrolidine ring.

The N-linked azetidine or pyrrolidine ring ($-NQ^1$) may be substituted at any substitutable position in the ring by Q^2. Preferably, the N-linked azetidine or pyrrolidine ring ($-NQ^1$) is substituted by Q^2 at a ring atom adjacent to the nitrogen atom linking the azetidine or pyrrolidine ring to the pyrimidine ring of the compounds of the invention.

Suitable values for any of the substituents herein, for example the 'R' groups (R^1 to R^{15}, R^{3a}, R^{3b}, R^{3c}, R^{3d} or R^{3e}) or for various groups within a Q^2 or Q^3 group include:

for halogeno:	fluoro, chloro, bromo and iodo;
for (C1-C6)alkyl:	methyl, ethyl, propyl, isopropyl, tert-butyl, n-pentyl and n-hexyl;
for (C2-C6)alkenyl:	vinyl, isopropenyl, allyl and but-2-enyl;
for (C2-C6)alkynyl:	ethynyl, 2-propynyl and but-2-ynyl;
for (C1-C6)alkoxy:	methoxy, ethoxy, propoxy, isopropoxy and butoxy;
for (C1-C6)alkoxy(C1-C6)alkoxy:	methoxymethoxy, methoxyethoxy, ethoxymethoxy, propoxymethoxy and butoxymethoxy;
for (C1-C6)alkoxy(C1-C6)alkyl:	methoxymethyl, methoxyethyl, ethoxymethyl, propoxymethyl and butoxymethyl;
for tri-[(C1-C4)alkyl]silyl	trimethylsilyl, triethylsilyl, dimethyl-ethylsilyl and methyl-diethylsilyl;
for (C1-C6)alkylthio:	methylthio, ethylthio and propylthio;
for (C1-C6)alkylamino:	methylamino, ethylamino, propylamino, isopropylamino and butylamino;
for di-[(C1-C6)alkyl]amino:	dimethylamino, diethylamino, N-ethyl-N-methylamino and N,N-diisopropylamino;
for amino(C1-C6)alkyl:	aminomethyl, aminoethyl, aminopropyl and aminobutyl;
for (C1-C6)alkylamino(C1-C6)alkyl:	methylaminomethyl, methylaminoethyl, methylaminopropyl, ethylaminomethyl, ethylaminoethyl, propylaminomethyl, isopropylaminoethyl and butylaminomethyl;
for di-[(C1-C6)alkyl]amino(C1-C6)alkyl:	dimethylaminomethyl, dimethylaminoethyl, dimethylaminobutyl, diethylaminomethyl, diethylaminoethyl, diethylaminopropyl, N-ethyl-N-methylaminomethyl, N-ethyl-N-methylaminomethyl and N,N-diisopropylaminoethyl;
for (C1-C6)alkylcarbonyl:	methylcarbonyl, ethylcarbonyl, propylcarbonyl and tert-butylcarbonyl;

for (C1-C6)alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;

for (C1-C6)alkylcarbamoyl: N-methylcarbamoyl, N-ethylcarbamoyl and N-propylcarbamoyl;

for di-[(C1-C6)alkyl]carbamoyl: N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl;

for (C3-C8)cycloalkyl: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl;

for (C3-C8)cycloalkyl(C1-C6)alkyl: cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl and cycloheptylmethyl;

for (C3-C8)cycloalkyl(C1-C6)alkoxy: cyclopropylmethoxy, cyclobutylmethoxy, cyclopentylmethoxy, cyclohexylmethoxy and cycloheptylmethoxy;

for (C3-C8)cycloalkylcarbonyl: cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl andcycloheptylcarbonyl;

for (C3-C8)cycloalkyl(C1-C6)alkylcarbonyl: cyclopropylmethylcarbonyl, cyclobutylmethylcarbonyl, cyclopentylmethylcarbonyl and cyclohexylmethylcarbonyl;

for (C3-C8)cycloalkylamino: cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino and cycloheptylamino;

for (C3-C8)cycloalkylamino(C1-C6)alkyl: cyclopropylaminomethyl, cyclopropylaminoethyl, cyclopropylaminopropyl, cyclobutylaminomethyl, cyclopentylaminoethyl, cyclopentylaminopropyl cyclohexylaminoethyl and cycloheptylaminoethyl;

for (C3-C8)cycloalkyl(C1-C6)alkylamino: cyclopropylmethylamino, cyclopropylethylamino, cyclopentylmethylamino and cyclohexylmethylamino;

for (C3-C8)cycloalkyl(C1-C6)alkylamino(C1-C6)alkyl: cyclopropylmethylaminomethyl, cyclopropylmethylaminoethyl, cyclopropylmethylaminopropyl, cyclopropylethylaminoethyl, cyclopropylethylaminobutyl, cyclopentylmethylaminoethyl, cyclopentylmethylaminobutyl and cyclohexylmethylaminoethyl;

for (C1-C6)alkoxyamino: methoxyamino, ethoxyamino, propoxyamino and butoxyamino;

for (C1-C6)alkanoyl: formyl, acetyl, propionyl, butyryl and isobuyryl;

for (C2-C6)alkanoylamino: acetamido and propionamido;

for (C1-C6)alkylsulfonyl: methylsulfonyl and ethylsulfonyl; and

for (C1-C6)alkylsulfinyl: methylsulfinyl and ethylsulfinyl.

Where the compounds according to the invention contain one or more asymmetrically substituted carbon atoms, the invention includes all stereoisomers, including enantiomers and diastereomers, and mixtures including racemic mixtures thereof.

Thus, it is to be understood that, insofar as certain of the compounds of formula (I) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. In particular, the compounds of formula (I) may have a chiral centre on the pyrrolidine or azetidine ring $-NQ^1$ at the carbon atom attached to the group Q^2). The present invention encompasses all such stereoisomers having activity as herein defined, for example the (2R) and (2S) isomers (in particular the (2S) isomers). It is further to be understood that in the names of chiral compounds (R,S) denotes any scalemic or racemic mixture while (R) and (S) denote the enantiomers. In the absence of (R,S), (R) or (S) in the name it is to be understood that the name refers to any scalemic or racemic mixture, wherein a scalemic mixture contains R and S enantiomers in any relative proportions and a racemic mixture contains R and S enantiomers in the ratio 50:50. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Racemates may be separated into individual enantiomers using known procedures (cf. Advanced Organic Chemistry: 3rd Edition: author J

March, pages 104 to 107). A suitable procedure involves formation of diastereomeric derivatives by reaction of the racemic material with a chiral auxiliary, followed by separation, for example by chromatography, of the diastereomers and then cleavage of the auxiliary species. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

It is to be understood that, insofar as certain of the compounds of formula (I) defined above may exist in tautomeric forms, the invention includes in its definition any such tautomeric form which possesses the above-mentioned activity. Thus, the invention relates to all tautomeric forms of the compounds of formula (I) which inhibit IGF-1R tyrosine kinase activity in a human or animal.

It is to be understood that certain compounds of formula (I) may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which inhibit IGF-1R tyrosine kinase activity in a human or animal.

It is also to be understood that certain compounds of formula (I) may exhibit polymorphism, and that the invention encompasses all such forms which inhibit IGF-1R tyrosine kinase activity in a human or animal.

The compounds according to the invention may be provided as pharmaceutically-acceptable salts. Suitable pharmaceutically-acceptable salts include base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, N-methylpiperidine, N-ethylpiperidine, procaine, dibenzylamine, N,N-dibenzylethylamine or amino acids for example lysine. In another aspect, where the compound is sufficiently basic, suitable salts include acid addition salts such as methanesulfonate, fumarate, hydrochloride, hydrobromide, citrate, maleate and salts formed with phosphoric and sulfuric acid.

In one aspect of the invention, q is 0, 1 or 2, especially 0 or 1, more especially 0.

In another aspect of the invention, q is 1.

In one aspect of the invention, a suitable value for R^1, when it is present, is a (C1-C6)alkyl group (for example a (C1-C4)alkyl group, such as methyl, ethyl, propyl, isopropyl or tert-butyl), a (C3-C8)cycloalkyl group (for example a (C3-C6)cycloalkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl) or a (C3-C8)cycloalkyl(C1-C6)alkyl group (for example a (C3-C6)cycloalkyl(C1-C4)alkyl group, such as cyclopropylmethyl),

each of which groups may be optionally substituted by one or more substituents independently selected from halogeno and (C1-C4)alkoxy.

In another aspect of the invention, a suitable value for R^1, when it is present, is a (C3-C8)cycloalkyl(C1-C6)alkyl group (such as cyclopropylmethyl, cyclopentylmethyl or cyclohexylmethyl), which group is optionally substituted by one or more substituents selected from halogeno and (1-4C)alkoxy.

In another aspect of the invention, a suitable value for R^1, when it is present, is a (C1-C6)alkyl group (for example a (C1-C4)alkyl group, such as methyl, ethyl, propyl, isopropyl or tert-butyl) or a (C3-C8)cycloalkyl group (for example a (C3-C6)cycloalkyl group, such as cyclopropyl, cyclopentyl or cyclohexyl), which group is optionally substituted by one or more substituents selected from halogeno and (1-4C)alkoxy. Another suitable value for R^1, when it is present, is an unsubstituted (C1-C6)alkyl group (for example a (C1-C4)alkyl group) or an unsubstituted (C3-C8)cycloalkyl group (for example a (C3-C6)cycloalkyl group).

In another aspect of the invention, a suitable value for R^1, when it is present, is an unsubstituted (C1-C2)alkyl group (for example methyl) or a cyano group.

In another aspect of the invention, a suitable value for R^1, when it is present, is an unsubstituted (C1-C4)alkyl group. For example, R^1 may be methyl, ethyl or tert-butyl, especially methyl or tert-butyl, more especially methyl.

In yet another aspect of the invention, a suitable value for R^1, when it is present, is methyl.

In yet another aspect of the invention, a suitable value for R^1, when it is present, is cyano.

In another aspect of the invention, a suitable value for R^1 is a (C3-C6)cycloalkyl group, such as cyclopropyl.

In one aspect of the invention, a suitable value for R^2 is hydrogen or trifluoromethyl.

In another aspect of the invention, a suitable value for R^2 is halogeno (such as fluoro, chloro, bromo or iodo, especially chloro or fluoro, more especially chloro).

In another aspect of the invention, a suitable value for R^2 is hydrogen.

In one aspect of the invention, R^3 is selected from hydrogen, hydroxy or halogeno, or from a (C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl, (C1-C6)alkoxy, (C3-C8)cycloalkyl(C1-C6)alkoxy, (C1-C6)alkylcarbonyl, (C1-C6)alkoxycarbonyl, amino, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, (C3-C8)cycloalkylamino, (C3-C8)cycloalkyl(C1-C6)alkylamino, (C1-

C6)alkoxyamino, carbamoyl, (C1-C6)alkylcarbamoyl, di-[(C1-C6)alkyl]carbamoyl, -C(O)R^{3b}, -OR^{3b}, -NHR^{3b}, -N[(C1-C6)alkyl]R^{3b}, -S(O)$_m$$R^{3a}$ or -N(R^{3c})C(O)R^{3a} group, wherein R^{3a} is selected from a (C1-C6)alkyl or (C1-C6)alkoxy group, m is 0, 1 or 2, R^{3b} is a saturated monocyclic 4-, 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur and R^{3c} is selected from hydrogen and (C1-C6)alkyl, or R^3 is a saturated monocyclic 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur, or R^3 is a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur, or R^3 is a 2,7-diazaspiro[3.5]nonane group. Each of these groups or rings within R^3 may be optionally substituted by one or more (for example one or two, particularly one) substituents independently selected from (C1-C6)alkyl, (C1-C6)alkoxy, (C1-C6)alkoxy(C1-C6)alkyl, (C1-C6)alkoxy(C1-C6)alkoxy, halogeno, hydroxy, trifluoromethyl, tri-[(C1-C4)alkyl]silyl, cyano, amino, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, amino(C1-C6)alkyl, (C1-C6)alkylamino(C1-C6)alkyl, di-[(C1-C6)alkyl]amino(C1-C6)alkyl, (C1-C6)alkoxycarbonyl, carbamoyl, (C1-C6)alkylcarbamoyl, di-[(C1-C6)alkyl]carbamoyl, (C1-C6)alkylthio, (C1-C6)alkylsulfonyl, (C1-C6)alkylsulfinyl, (C1-C6)alkanoyl, an alkanoylamino group -N(R^{3d})C(O)R^{3e} wherein R^{3d} is selected from hydrogen and (C1-C6)alkyl and R^{3e} is selected from a (C1-C6)alkyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl or (C1-C6)alkoxy group, or a saturated monocyclic 3-, 4-, 5-, 6- or 7-membered ring, which ring may optionally comprise one or more heteroatoms selected from nitrogen, oxygen and sulfur, any of which substituents may be optionally substituted by one or more (for example one or two, particularly one) (C1-C4)alkyl, hydroxy or cyano groups. Any saturated monocyclic ring within R^3 optionally bears 1 or 2 oxo or thioxo substituents.

In another aspect of the invention, R^3 is selected from hydrogen, hydroxy or halogeno, or from a (C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C3-C8)cycloalkyl, (C1-C6)alkoxy, (C1-C6)alkoxycarbonyl, amino, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, (C3-C8)cycloalkylamino, carbamoyl, (C1-C6)alkylcarbamoyl, di-[(C1-C6)alkyl]carbamoyl, -C(O)R^{3b}, -OR^{3b}, -NHR^{3b} or -S(O)$_m$$R^{3a}$ group, wherein R^{3a} is a (C1-C6)alkyl group, m is 0 and R^{3b} is a saturated monocyclic 4-, 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur, or R^3 is a saturated monocyclic 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen and oxygen, or R^3 is a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen and oxygen. Each of these

groups or rings within R^3 may be optionally substituted by one or more (for example one or two, particularly one) substituents independently selected from (C1-C6)alkyl, (C1-C6)alkoxy, (C1-C6)alkoxy(C1-C6)alkyl, (C1-C6)alkoxy(C1-C6)alkoxy, halogeno, hydroxy, trifluoromethyl, tri-[(C1-C4)alkyl]silyl, amino, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, amino(C1-C6)alkyl, (C1-C6)alkoxycarbonyl, carbamoyl, (C1-C6)alkylcarbamoyl, (C1-C6)alkylthio, (C1-C6)alkylsulfonyl, (C1-C6)alkanoyl, an alkanoylamino group -$N(R^{3d})C(O)R^{3e}$ wherein R^{3d} is selected from hydrogen and (C1-C6)alkyl and R^{3e} is selected from a (C1-C6)alkyl or (C1-C6)alkoxy group, or a saturated monocyclic 3-, 4-, 5- or 6-membered ring, which ring may optionally comprise one or more heteroatoms selected from nitrogen, oxygen and sulfur, any of which substituents may be optionally substituted by one or more (for example one or two, particularly one) (C1-C4)alkyl, hydroxy or cyano groups. Any saturated monocyclic ring within R^3 optionally bears 1 or 2 oxo substituents.

In another aspect of the invention, R^3 is selected from hydrogen, hydroxy or halogeno, or from a (C1-C4)alkyl, (C2-C4)alkenyl, (C2-C4)alkynyl, (C1-C3)alkoxy, amino, (C1-C3)alkylamino, di-[(C1-C3)alkyl]amino, (C3-C6)cycloalkylamino, carbamoyl, (C1-C3)alkylcarbamoyl, di-[(C1-C3)alkyl]carbamoyl, -$C(O)R^{3b}$, -OR^{3b}, -NHR^{3b} or -$S(O)_mR^{3a}$ group, wherein R^{3a} is a (C1-C3)alkyl group, m is 0 and R^{3b} is a saturated monocyclic 4-, 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur, or R^3 is a saturated monocyclic 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen and oxygen, or R^3 is a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen and oxygen. Each of these groups or rings within R^3 may be optionally substituted by one or more substituents as defined above, in particular by one or more (for example one or two, particularly one) substituents independently selected from (C1-C3)alkyl, (C1-C3)alkoxy, (C1-C3)alkoxy(C1-C3)alkyl, (C1-C3)alkoxy(C1-C3)alkoxy, halogeno, hydroxy, trifluoromethyl, amino, (C1-C3)alkylamino, di-[(C1-C3)alkyl]amino, amino(C1-C3)alkyl, carbamoyl, (C1-C3)alkylcarbamoyl, (C1-C3)alkylthio, (C1-C3)alkylsulfonyl, (C1-C3)alkanoyl, an alkanoylamino group -$N(R^{3d})C(O)R^{3e}$ wherein R^{3d} is selected from hydrogen and (C1-C3)alkyl and R^{3e} is selected from a (C1-C3)alkyl or (C1-C3)alkoxy group, or a saturated monocyclic 3-, 4-, 5- or 6-membered ring, which ring may optionally comprise one or more heteroatoms selected from nitrogen, oxygen and sulfur, any of which substituents may be optionally substituted by one or more (for example one or two, particularly one) (C1-

C2)alkyl, hydroxy or cyano groups. Any saturated monocyclic ring within R^3 optionally bears 1 oxo substituent.

In one aspect of the invention, R^3, when it is substituted, may be substituted by one or more (for example, one, two or three, particularly one or two, more particularly one) substituents independently selected from (C1-C6)alkoxy (such as methoxy or ethoxy), (C1-C6)alkoxy(C1-C6)alkoxy (such as methoxyethoxy) or a saturated monocyclic 3-, 4-, 5-, 6- or 7-membered (for example 4-, 5-, 6- or 7-membered) ring, which ring may optionally comprise one or more heteroatoms selected from nitrogen, oxygen and sulfur (such as cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, dioxanyl, morpholinyl, tetrahydrofuranyl or piperazinyl).

In another aspect of the invention, R^3, when it is substituted, may be substituted by one or more (for example, one or two, particularly one) substituents independently selected from (C1-C6)alkyl, (C1-C6)alkoxy, halogeno, hydroxy, trifluoromethyl, amino, (C1-C6)alkylamino and di-[(C1-C6)alkyl]amino, or a saturated monocyclic 3-, 4-, 5-, 6- or 7-membered (for example 4-, 5-, 6- or 7-membered) ring, which ring may optionally comprise one or more heteroatoms selected from nitrogen, oxygen and sulfur.

In another aspect of the invention, when R^3 carries a substituent that is a saturated monocyclic 3-, 4-, 5-, 6- or 7-membered (for example 4-, 5-, 6- or 7-membered) ring, which ring may optionally comprise one or more heteroatoms selected from nitrogen, oxygen and sulfur, that ring preferably comprises nitrogen and, optionally, one or two additional heteroatoms selected from nitrogen, oxygen and sulfur. For example, the saturated monocyclic 3-, 4-, 5-, 6- or 7-membered ring substituent on R^3 may be pyrrolidine.

In another aspect of the invention, R^3 is selected from hydrogen or from a (C1-C4)alkyl, (C1-C3)alkoxy or (C3-C5)cycloalkyl group, or R^3 is a saturated monocyclic 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen and oxygen. Each of these groups or rings within R^3 may be optionally substituted by one or more (for example one or two, particularly one) substituents as defined above, in particular by one or more substituents independently selected from hydroxy and (C1-C3)alkoxy.

In another aspect of the invention, R^3 is selected from hydrogen and halogeno, or from a (C1-C4)alkyl or (C1-C3)alkoxy group, or R^3 is a saturated monocyclic 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen and oxygen. Each of these groups or rings within R^3 may be optionally substituted by one or more (for

example one or two, particularly one) substituents as defined above, in particular by one or more substituents independently selected from hydroxy and (C1-C3)alkoxy.

In yet another aspect of the invention, R^3 is selected from halogeno, or from a (C1-C4)alkyl or (C1-C3)alkoxy group, or R^3 is a saturated monocyclic 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen and oxygen. Each of these groups or rings within R^3 may be optionally substituted by one or more (for example one or two, particularly one) substituents as defined above, in particular by one or more substituents independently selected from hydroxy and (C1-C3)alkoxy.

In another aspect of the invention, R^3 is selected from hydrogen or halogeno, or from a (C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C1-C6)alkoxy, (C1-C6)alkylcarbonyl, (C1-C6)alkoxycarbonyl, amino, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, carbamoyl, $-C(O)R^{3b}$, $-OR^{3b}$, $-SR^{3b}$, $-NHR^{3b}$, $-N[(C1-C6)alkyl]R^{3b}$ or $-S(O)_mR^{3a}$ group (wherein m, R^{3a} and R^{3b} are as defined above), or R^3 is a saturated monocyclic 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur, each of which groups or rings may be optionally substituted by one or more (for example one or two, particularly one) substituents as defined hereinbefore.

In another aspect of the invention, R^3 is selected from hydrogen or from a substituted or unsubstituted group selected from (C1-C6)alkyl (for example (C1-C4)alkyl, such as methyl, ethyl, propyl, isopropyl or tert-butyl), (C3-C8)cycloalkyl (for example(C3-C6)cycloalkyl, such as cyclopropyl, cyclopentyl or cyclohexyl), (C3-C8)cycloalkyl(C1-C6)alkyl (for example (C3-C6)cycloalkyl(C1-C4)alkyl, such as cyclopropylmethyl), (C1-C6)alkoxy (for example (C1-C4)alkoxy, such as methoxy, ethoxy, propoxy, isopropoxy and butoxy), (C1-C6)alkylcarbonyl (for example (C1-C4alkylcarbonyl, such as methylcarbonyl), (C3-C8)cycloalkylcarbonyl (for example (C3-C6)cycloalkylcarbonyl, such as cyclopropylcarbonyl), (C3-C8)cycloalkyl(C1-C6)alkylcarbonyl (for example (C3-C6)cycloalkyl(C1-C4)alkylcarbonyl, such as cyclopropylmethylcarbonyl), (C1-C6)alkoxycarbonyl (for example (C1-C4)alkoxycarbonyl, such as methoxycarbonyl), (C1-C6)alkylamino (for example (C1-C4)alkylamino, such as methylamino or ethylamino), (C3-C8)cycloalkylamino, (C3-C8)cycloalkyl(C1-C6)alkylamino, (C1-C6)alkoxyamino or $-S(O)_mR^{3a}$ (wherein m and R^{3a} are as defined above).

In another aspect of the invention, suitable values for R^3 include, for example, hydrogen, hydroxy, chloro, fluoro or iodo, or a methyl, ethyl, n-propyl, iso-propyl, n-butyl, tert-butyl, ethenyl, propenyl, butenyl, pentenyl, ethynyl, propynyl, butynyl, methoxy, ethoxy,

propoxy, tert-butoxy, cyclopropyl, cyclobutyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, cyclobutylamino, cyclohexylamino, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N-butylcarbamoyl, N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl, pyrrolidinylcarbonyl, morpholinylcarbonyl, azetidinylcarbonyl, methylthio, ethylthio, piperidinylamino, tetrahydropyranylamino, tetrahydropyranyloxy, pyrrolidinyl, morpholinyl, piperazinyl, oxadiazolyl or 2,7-diazaspiro[3.5]nonan-7-yl group, each of which groups or rings may be optionally substituted by one or more (for example one or two, particularly one) substituents as defined above.

In yet another aspect of the invention, suitable values for R^3 include, for example, hydrogen, hydroxy, chloro, fluoro, bromo, iodo, methyl, ethyl, propyl, iso-propyl, butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, trifluoromethyl, hydroxymethyl, methoxymethyl, ethoxymethyl, (2-methoxyethoxy)methyl, aminomethyl, methylaminomethyl, ethylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, pyrrolidin-1-ylmethyl, 2-hydroxyethyl, 2-methoxyethyl, 2-ethoxyethyl, 2-(ethoxycarbonyl)ethyl, 2-(N-methylcarbamoyl)ethyl, 3-hydroxypropyl, 3-methoxypropyl, 3-ethoxypropyl, 3-aminoprop-1-yl, 3-N,N-dimethylaminopropyl, 3-(tert-butoxycarbonylamino)prop-1-yl, 3-pyrrolidin-1-ylpropyl, ethenyl, propenyl, butenyl, pentenyl, 3-hydroxyprop-1-en-1-yl, 3-aminoprop-1-en-1-yl, 2-(methoxycarbonyl)ethen-1-yl, 3-(tert-butoxycarbonylamino)prop-1-en-1-yl, ethynyl, propynyl, butynyl, pentynyl, 3-hydroxyprop-1-yn-1-yl, 3-methoxyprop-1-yn-1-yl, 2-(trimethylsilyl)ethynyl, 3-aminoprop-1-yn-1-yl, 3-methylaminoprop-1-yn-1-yl, 3-(dimethylamino)prop-1-yn-1-yl, 3-(N-methylacetamido)prop-1-yn-1-yl, 3-acetamidoprop-1-yn-1-yl, methoxy, ethoxy, propoxy, butoxy, pentoxy, (5-oxopyrrolidin-2-yl)methoxy, tetrahydrofuran-3-ylmethoxy, 2-hydroxyethoxy, 2-ethoxyethoxy, 2-(2-hydroxyethoxy)ethoxy, 2-methoxyethoxy, (2-methoxyethoxy)ethoxy, 2-{N-[2-hydroxyethyl]-N-methyl-amino}ethoxy, 2-morpholinoethoxy, 2-(2-oxopyrrolidin-1-yl)ethoxy, 2-(imidazolid-2-on-1-yl)ethoxy, 3-hydroxypropyloxy, 2-hydroxyprop-1-yloxy, 3-methoxyprop-1-yloxy, 2-methoxyprop-1-yloxy, 3-morpholinoprop-1-yloxy, 3-(methylthio)prop-1-yloxy, 3-(methylsulfonyl)propyl-1-oxy, methoxycarbonyl, tert-butoxycarbonyl, N-(tert-butoxycarbonyl)amino, methylamino, 2-methoxyethylamino, 2-aminoethylamino, 2-(dimethylamino)ethylamino, (N-2-methoxyethyl)-N-methylamino, 3-isopropoxyprop-1-ylamino, 2-(2-hydroxyethoxy)ethylamino, 2-(acetoamido)ethylamino, 2-(morpholin-4-yl)ethylamino, 2-methylprop-1-ylamino, 2-

hydroxyprop-1-ylamino, 3-methoxypropylamino, 3-ethoxypropylamino, 2-isopropoxyethylamino, tetrahydrofuran-2-ylmethylamino, dimethylamino, N-(2-hydroxyethyl)-N-ethylamino, cyclopropylamino, cyclobutylamino, cyclopentylamino, 4-methylcyclohexylamino, 4-hydroxycyclohexylamino, carbamoyl, N-hydroxycarbamoyl, N-cyclopropylcarbamoyl, N-cyclopentylcarbamoyl, N-aminocarbamoyl, N-(acetylamino)carbamoyl, N-methylcarbamoyl, 2-hydroxyethylcarbamoyl, N-(2-hydroxypropyl)carbamoyl, N-(2,3-dihydroxypropyl)carbamoyl, N-(4-hydroxybutyl)carbamoyl, N-(2-methoxyethyl)carbamoyl, N-(2-(acetylamino)ethyl)carbamoyl, N-[2-(2-hydroxyethoxy)ethyl]carbamoyl, N-(carbamoylmethyl)carbamoyl, N-[2-(methylthio)ethyl]carbamoyl, N-(2-methoxyethyl)-N-methylcarbamoyl, pyrrolidin-1-ylcarbonyl, morpholinocarbonyl, azetidin-1-ylcarbonyl, (3-hydroxypyrrolidin-1-yl)carbonyl, methylthio, ethylthio, propylthio, 2,2,6,6-tetramethylpiperidin-4-ylamino, 4-tetrahydropyranylamino, tetrahydropyran-4-yloxy, pyrrolidin-1-yl, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-ethylpiperazin-1-yl, 4-isopropylpiperazin-1-yl, 4-(2-hydroxyethyl)piperazin-1-yl, 4-(3-hydroxypropyl)piperazin-1-yl, 4-(2-methoxyethyl)piperazin-1-yl, 4-(2-aminoethyl)piperazin-1-yl, 4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl, 4-(2-cyanoethyl)piperazin-1-yl, 4-(tert-butoxycarbonyl)piperazin-1-yl, 1-formyl-piperazin-4-yl, 4-acetylpiperazin-1-yl, 4-(ethylsulfonyl)piperazin-1-yl, 4-aminopiperidin-1-yl, 4-(N-tert-butoxycarbonylamino)piperidin-1-yl, 3-hydroxypyrrolidin-1-yl, 3-dimethylamino-pyrrolidin-1-yl, cis-3,4-dihydroxypyrrolidin-1-yl, 5-methyl-[1,3,4]-oxadiazol-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl and (tert-butoxycarbonyl)-2,7-diazaspiro[3.5]nonan-7-yl.

Further suitable values for R^3 include, for example, hydrogen, hydroxy, chloro, iodo, methyl, ethyl, propyl, cyclopropyl, trifluoromethyl, hydroxymethyl, methoxymethyl, ethoxymethyl, (2-methoxyethoxy)methyl, aminomethyl, methylaminomethyl, morpholinomethyl, 4-methylpiperazin-1-ylmethyl, pyrrolidin-1-ylmethyl, 2-methoxyethyl, 2-(ethoxycarbonyl)ethyl, 2-(N-methylcarbamoyl)ethyl, 3-hydroxypropyl, 3-methoxypropyl, 3-aminoprop-1-yl, 3-N,N-dimethylaminopropyl, 3-(tert-butoxycarbonylamino)prop-1-yl, 3-pyrrolidin-1-ylpropyl, ethenyl, pent-3-en-1-yl, 3-hydroxyprop-1-en-1-yl, 3-aminoprop-1-en-1-yl, 2-(methoxycarbonyl)ethen-1-yl, 3-(tert-butoxycarbonylamino)prop-1-en-1-yl, ethynyl, 3-hydroxyprop-1-yn-1-yl, 3-methoxyprop-1-yn-1-yl, 2-(trimethylsilyl)ethynyl, 3-aminoprop-1-yn-1-yl, 3-methylaminoprop-1-yn-1-yl, 3-(dimethylamino)prop-1-yn-1-yl, 3-(N-methylacetamido)prop-1-yn-1-yl, 3-acetamidoprop-1-yn-1-yl, methoxy, ethoxy, (5-

oxopyrrolidin-2-yl)methoxy (for example (2S)-(5-oxopyrrolidin-2-yl)methoxy or (2R)-(5-oxopyrrolidin-2-yl)methoxy), tetrahydrofuran-3-ylmethoxy, 2-hydroxyethoxy, 2-ethoxyethoxy, 2-(2-hydroxyethoxy)ethoxy, 2-methoxyethoxy, (2-methoxyethoxy)ethoxy, 2-{N-[2-hydroxyethyl]-N-methyl-amino}ethoxy, 2-morpholinoethoxy, 2-(2-oxopyrrolidin-1-yl)ethoxy, 2-(imidazolid-2-on-1-yl)ethoxy, 3-hydroxypropyloxy, 2-hydroxyprop-1-yloxy (for example (2R)-2-hydroxyprop-1-yloxy), 3-methoxyprop-1-yloxy, 2-methoxyprop-1-yloxy (for example (2S)-2-methoxyprop-1-yloxy), 3-morpholinoprop-1-yloxy, 3-(methylthio)prop-1-yloxy, 3-(methylsulfonyl)propyl-1-oxy, methoxycarbonyl, N-(tert-butoxycarbonyl)amino, methylamino, 2-methoxyethylamino, 2-aminoethylamino, 2-(dimethylamino)ethylamino, (N-2-methoxyethyl)-N-methylamino, 3-isopropoxyprop-1-ylamino, 2-(2-hydroxyethoxy)ethylamino, 2-(acetoamido)ethylamino, 2-(morpholin-4-yl)ethylamino, 2-methylprop-1-ylamino, 2-hydroxyprop-1-ylamino (for example (2*R*)-2-hydroxyprop-1-ylamino or (2S)-2-hydroxyprop-1-ylamino), 3-methoxypropylamino, 3-ethoxypropylamino, 2-isopropoxyethylamino, tetrahydrofuran-2-ylmethylamino (for example (2R)-tetrahydrofuran-2-ylmethylamino), dimethylamino, N-(2-hydroxyethyl)-N-ethylamino, cyclobutylamino, 4-methylcyclohexylamino, 4-hydroxycyclohexylamino, carbamoyl, N-hydroxycarbamoyl, N-cyclopropylcarbamoyl, N-cyclopentylcarbamoyl, N-aminocarbamoyl, N-(acetylamino)carbamoyl, N-methylcarbamoyl, 2-hydroxyethylcarbamoyl, N-(2-hydroxypropyl)carbamoyl (for example N-((R)-2-hydroxypropyl)carbamoyl), N-(2,3-dihydroxypropyl)carbamoyl (for example N-((2R)-2,3-dihydroxypropyl)carbamoyl), N-(4-hydroxybutyl)carbamoyl, N-(2-methoxyethyl)carbamoyl, N-(2-(acetylamino)ethyl)carbamoyl, N-[2-(2-hydroxyethoxy)ethyl]carbamoyl, N-(carbamoylmethyl)carbamoyl, N-[2-(methylthio)ethyl]carbamoyl, N-(2-methoxyethyl)-N-methylcarbamoyl, pyrrolidin-1-ylcarbonyl, morpholinocarbonyl, azetidin-1-ylcarbonyl, (3-hydroxypyrrolidin-1-yl)carbonyl (for example (3R)-3-hydroxypyrrolidin-1-ylcarbonyl), methylthio, 2,2,6,6-tetramethylpiperidin-4-ylamino, 4-tetrahydropyranylamino, tetrahydropyran-4-yloxy, pyrrolidin-1-yl, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-ethylpiperazin-1-yl, 4-isopropylpiperazin-1-yl, 4-(2-hydroxyethyl)piperazin-1-yl, 4-(3-hydroxypropyl)piperazin-1-yl, 4-(2-methoxyethyl)piperazin-1-yl, 4-(2-aminoethyl)piperazin-1-yl, 4-[2-(2-hydroxyethoxy)ethyl]piperazin-1-yl, 4-(2-cyanoethyl)piperazin-1-yl, 4-(tert-butoxycarbonyl)piperazin-1-yl, 1-formyl-piperazin-4-yl, 4-acetylpiperazin-1-yl, 4-(ethylsulfonyl)piperazin-1-yl, 4-aminopiperidin-1-yl, 4-(N-tert-butoxycarbonylamino)piperidin-1-yl, 3-hydroxypyrrolidin-1-yl (for example (3*R*)-3-

hydroxypyrrolidin-1-yl), 3-dimethylamino-pyrrolidin-1-yl (for example (3*R*)-3-dimethylamino-pyrrolidin-1-yl), cis-3,4-dihydroxypyrrolidin-1-yl, 5-methyl-[1,3,4]-oxadiazol-2-yl, 2,7-diazaspiro[3.5]nonan-7-yl and (tert-butoxycarbonyl)-2,7-diazaspiro[3.5]nonan-7-yl.

Yet further suitable values for R^3 include, for example, hydrogen, chloro, iodo, methyl, ethyl, trifluoromethyl, hydroxymethyl, methoxymethyl, ethoxymethyl, (2-methoxyethoxy)methyl, morpholinomethyl, 3-hydroxypropyl, 3-methoxypropyl, 3-N,N-dimethylaminopropyl, ethenyl, 3-hydroxyprop-1-en-1-yl, ethynyl, 3-hydroxyprop-1-yn-1-yl, 3-methoxyprop-1-yn-1-yl, 3-aminoprop-1-yn-1-yl, 3-methylaminoprop-1-yn-1-yl, 3-(dimethylamino)prop-1-yn-1-yl, 3-(N-methylacetamido)prop-1-yn-1-yl, 3-acetamidoprop-1-yn-1-yl, methoxy, ethoxy, (5-oxopyrrolidin-2-yl)methoxy (for example (2S)-(5-oxopyrrolidin-2-yl)methoxy or (2R)-(5-oxopyrrolidin-2-yl)methoxy), tetrahydrofuran-3-ylmethoxy, 2-hydroxyethoxy, 2-ethoxyethoxy, 2-(2-hydroxyethoxy)ethoxy, 2-methoxyethoxy, (2-methoxyethoxy)ethoxy, 2-{N-[2-hydroxyethyl]-N-methyl-amino}ethoxy, 2-morpholinoethoxy, 2-(2-oxopyrrolidin-1-yl)ethoxy, 2-(imidazolid-2-on-1-yl)ethoxy, 3-hydroxypropyloxy, 2-hydroxyprop-1-yloxy (for example (2R)-2-hydroxyprop-1-yloxy), 3-methoxyprop-1-yloxy, 2-methoxyprop-1-yloxy (for example (2S)-2-methoxyprop-1-yloxy), 3-morpholinoprop-1-yloxy, 3-(methylthio)prop-1-yloxy, 3-(methylsulfonyl)propyl-1-oxy, methylamino, 2-methoxyethylamino, 2-(methoxyethyl)amino, 2-(2-hydroxyethoxy)ethylamino, 2-(morpholin-4-yl)ethylamino, 2-methylprop-1-ylamino, 2-hydroxyprop-1-ylamino (for example (2*R*)-2-hydroxyprop-1-ylamino or (2S)-2-hydroxyprop-1-ylamino), 3-methoxypropylamino, 3-ethoxypropylamino, 2-isopropoxyethylamino, tetrahydrofuran-2-ylmethylamino (for example (2R)-tetrahydrofuran-2-ylmethylamino), dimethylamino, N-(2-hydroxyethyl)-N-ethylamino, cyclobutylamino, carbamoyl, N-cyclopropylcarbamoyl, N-methylcarbamoyl, 2-hydroxyethylcarbamoyl, N-(2-hydroxypropyl)carbamoyl (for example N-((R)-2-hydroxypropyl)carbamoyl), N-(2-methoxyethyl)carbamoyl, N-[2-(methylthio)ethyl]carbamoyl, pyrrolidin-1-ylcarbonyl, azetidin-1-ylcarbonyl, methylthio, 4-tetrahydropyranylamino, tetrahydropyran-4-yloxy, pyrrolidin-1-yl, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-ethylpiperazin-1-yl, 4-isopropylpiperazin-1-yl, 4-(2-hydroxyethyl)piperazin-1-yl, 4-(3-hydroxypropyl)piperazin-1-yl, 4-(2-methoxyethyl)piperazin-1-yl, 4-(2-cyanoethyl)piperazin-1-yl, , 4-acetylpiperazin-1-yl, 4-(ethylsulfonyl)piperazin-1-yl, 3-hydroxypyrrolidin-1-yl (for example (3*R*)-3-

hydroxypyrrolidin-1-yl), 3-dimethylamino-pyrrolidin-1-yl (for example (3*R*)-3-dimethylamino-pyrrolidin-1-yl) and 1-formyl-piperazin-4-yl.

In another aspect of the invention, R^3 is selected from chloro, methyl, ethyl, methoxy and morpholino.

In yet another aspect of the invention, R^3 is selected from chloro, methyl, methoxy and morpholino.

In yet another aspect of the invention, R^3 is methyl.

In yet another aspect of the invention, R^3 is methoxy.

In one aspect of the invention, $-NQ^1$ is a N-linked pyrrolidinyl group.

In one aspect of the invention, a suitable value for Q^2 is a 5- or 6-membered heteroaromatic ring comprising one, two, three or four ring heteroatoms, which may be the same or different, selected from nitrogen, oxygen and sulfur. For example, suitable values for Q^2 include thienyl, pyrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, triazolyl, tetrazolyl, imidazolyl, pyrazinyl, pyridazinyl, pyrimidinyl and pyridyl.

In another aspect of the invention, a suitable value for Q^2 is a 5- or 6-membered heteroaromatic ring comprising one or two ring heteroatoms, which may be the same or different, selected from nitrogen and oxygen. For example, suitable values for Q^2 include pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, imidazolyl, oxazolyl, tetrazolyl and isoxazolyl (especially tetrazolyl and isoxazolyl).

In another aspect of the invention, a suitable value for Q^2 is a 5- or 6-membered (especially 5-membered) heteroaromatic ring comprising a nitrogen and an oxygen ring heteroatom, for example an isoxazolyl ring (such as isoxazol-5-yl).

In yet another aspect of the invention, a suitable value for Q^2 is a 5- or 6-membered heteroaromatic ring comprising from one to four nitrogen ring heteroatoms. For example, suitable values for Q^2 include pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, pyrazinyl, pyridazinyl, pyrimidinyl and pyridyl.

The ring Q^2 may suitably be linked to the N-linked azetidine or pyrrolidine ring ($-NQ^1$) through any available ring atom, for example it may be linked via. a ring carbon or a ring nitrogen atom. In particular, Q^2 may be linked to the N-linked azetidine or pyrrolidine ring ($-NQ^1$) via. a ring carbon atom, for example via. a ring carbon atom that is adjacent to a heteroatom.

In addition to being substituted by Q^3, Q^2 is optionally substituted by at least one substituent (for example, one, two, three or four substituents), which may be the same or

different, independently selected from (C1-C6)alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) and (C1-C6)alkoxy (such as methoxy, ethoxy, n-propoxy, n-butoxy, tert-butoxy, n-pentoxy or n-hexoxy) (either of which (C1-C6)alkyl and (C1-C6)alkoxy substituent groups may be optionally substituted by at least one substituent, for example one, two, three or four substituents, independently selected from halogeno (such as fluoro, chloro, bromo or iodo), amino, hydroxy and trifluoromethyl), halogeno (such as fluoro, chloro, bromo or iodo), nitro, cyano, $-NR^4R^5$, carboxy, hydroxy, (C2-C6)alkenyl (such as ethenyl), (C3-C8)cycloalkyl (such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), (C3-C8)cycloalkyl(C1-C6)alkyl (such as cyclopropylmethyl), (C1-C4)alkoxycarbonyl (such as methoxycarbonyl or ethoxycarbonyl), (C1-C4)alkylcarbonyl (such as methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl or n-butylcarbonyl), (C2-C6)alkanoylamino (such as acetamido or propionamido), phenylcarbonyl, $-S(O)_p$(C1-C4)alkyl (such as methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl or ethylsulfonyl), $-C(O)NR^6R^7$ and $-SO_2NR^8R^9$ (where p, R^4, R^5, R^6, R^7, R^8 and R^9 are as defined above).

In one aspect of the invention, R^4, R^5, R^6, R^7, R^8 and R^9 may each suitably independently represent hydrogen or (C1-C4)alkyl (such as methyl, ethyl, propyl or butyl), or suitably R^4 and R^5, or R^6 and R^7, or R^8 and R^9, when taken together with the nitrogen atom to which they are attached, may each independently form a saturated heterocyclic ring such as pyrrolidinyl or piperidinyl.

In one aspect of the invention, Q^2 is substituted by Q^3 and is optionally substituted by at least one substituent independently selected from (C1-C6)alkyl, (C1-C6)alkoxy, halogeno and (C3-C8)cycloalkyl.

In another aspect of the invention, Q^2 is substituted only by Q^3.

In one aspect of the invention, a suitable value for Q^3 is a substituted or unsubstituted (C1-C6)alkyl (such as methyl, ethyl, propyl or butyl), (C3-C8)cycloalkyl (such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl) or (C3-C8)cycloalkyl(C1-C6)alkyl (such as cyclopropylmethyl) group, or a saturated or unsaturated 5- or 6-membered monocyclic ring which may comprise at least one ring heteroatom (for example, one, two, three or four heteroatoms) selected from nitrogen, oxygen and sulfur (such as phenyl, pyridyl, imidazolyl, isoxazolyl, pyrazolyl, furyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl , thiazolyl, oxazolyl, isothiazolyl, triazolyl, tetrahydrofuranyl or thienyl, especially pyridyl, pyrazinyl, thiazolyl, tetrahydrofuranyl or pyrimidinyl, more especially pyridyl, pyrazinyl or thiazolyl).

In another aspect of the invention, a suitable value for Q^3 is a substituted or unsubstituted (C1-C6)alkyl or (C3-C8)cycloalkyl group, or a substituted or unsubstituted saturated or unsaturated 5- or 6-membered monocyclic ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulfur. For example, suitable values for Q^3 include a substituted or unsubstituted group selected from methyl, cyclopropyl, pyridyl, pyrazinyl, thiazolyl, tetrahydrofuranyl or pyrimidinyl.

In yet another aspect of the invention, a suitable value for Q^3 is a substituted or unsubstituted (C1-C4)alkyl (such as methyl) or (C3-C6)cycloalkyl (such as cyclopropyl) group, or an optionally substituted unsaturated 5- or 6-membered monocyclic ring comprising one or two ring heteroatoms, which may be the same or different, selected from nitrogen, oxygen and sulfur, such as imidazolyl, isoxazolyl, pyrazolyl, furyl, pyrazinyl (such as pyrazin-2-yl), pyridazinyl, pyrimidinyl (such as pyrimidin-2-yl), pyrrolyl, oxazolyl, isothiazolyl, triazolyl, tetrahydrofuranyl or thienyl, especially pyridyl (such as pyrid-2-yl or pyrid-3-yl) or thiazolyl (such as thiazol-2-yl or thiazol-4-yl) or tetrahydrofuranyl (such as tetrahydrofuran-3-yl).

In yet another aspect of the invention, a suitable value for Q^3 is an optionally substituted unsaturated 5- or 6-membered monocyclic ring comprising one or two ring nitrogen atoms, such as pyridyl (especially pyrid-2-yl or pyrid-3-yl, more especially pyrid-2-yl), pyrazinyl (especially pyrazin-2-yl) or pyrimidinyl (especially pyrimidin-2-yl). A particular value for Q^3 in this aspect of the invention is pyridyl (especially pyrid-2-yl or pyrid-3-yl, more especially pyrid-2-yl).

In yet another aspect of the invention, a suitable value for Q^3 is an optionally substituted unsaturated 5- or 6-membered monocyclic ring comprising one or two ring heteroatoms, which may be the same or different, selected from nitrogen, oxygen and sulfur (especially selected from nitrogen and sulfur), such as imidazolyl, isoxazolyl, pyrazolyl, furyl, pyrazinyl (especially pyrazin-2-yl), pyridazinyl, pyrimidinyl (especially pyrimidin-2-yl), pyrrolyl, oxazolyl, isothiazolyl, triazolyl, tetrahydrofuranyl or thienyl, especially pyridyl (preferably pyrid-2-yl or pyrid-3-yl) or thiazolyl (especially thiazol-2-yl or thiazol-4-yl) or tetrahydrofuranyl (especially tetrahydrofuran-3-yl). Particular values for Q^3 in this aspect of the invention include pyridyl (especially pyrid-2-yl or pyrid-3-yl, more especially pyrid-2-yl), thiazolyl (especially thiazol-2-yl or thiazol-4-yl, more especially thiazol-2-yl) or pyrazinyl (especially pyrazin-2-yl).

In still yet another aspect of the invention, a suitable value for Q^3 is an optionally substituted unsaturated 5- or 6-membered monocyclic ring comprising one or two ring heteroatoms, which may be the same or different, selected from nitrogen, oxygen and sulfur (especially selected from nitrogen and sulfur), such as pyrazinyl (especially pyrazin-2-yl), pyrimidinyl (especially pyrimidin-2-yl), pyridyl (especially pyrid-2-yl or pyrid-3-yl) or thiazolyl (especially thiazol-2-yl).

In one aspect of the invention, suitable substituents for Q^3, when it is substituted, include one or more (for example, one, two, three or four) substituents independently selected from (C1-C6)alkyl and (C1-C6)alkoxy (either of which (C1-C6)alkyl and (C1-C6)alkoxy substituent groups may be optionally substituted by at least one substituent (for example, one, two, three or four substituents) independently selected from halogeno, amino, hydroxy and trifluoromethyl), halogeno, nitro, cyano, $-NR^{10}R^{11}$, carboxy, hydroxy, (C2-C6)alkenyl, (C3-C8)cycloalkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C2-C6)alkanoylamino, phenylcarbonyl, $-S(O)_n$(C1-C6)alkyl, $-C(O)NR^{12}R^{13}$ and $-SO_2NR^{14}R^{15}$ (where n, R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are as defined above).

In another aspect of the invention, suitable substituents for Q^3, when it is substituted, include one or more (for example, one or two, particularly one) substituents independently selected from (C1-C4)alkyl, (C1-C4)alkoxy, cyano and $-NR^{10}R^{11}$ (where R^{10} and R^{11} are as defined above).

In another aspect of the invention, suitable substituents for Q^3, when it is substituted, include one or more (for example, one or two, particularly one) substituents independently selected from (C1-C4)alkyl (such as methyl), (C1-C4)alkoxy (such as methoxy) and cyano.

In another aspect of the invention, suitable substituents for Q^3, when it is substituted, include one or more (for example, one or two, particularly one) substituents independently selected from (C1-C4)alkyl and (C1-C4)alkoxy, especially (C1-C6)alkoxy.

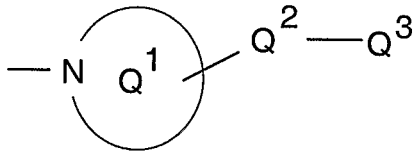
Suitably, R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} may each independently represent hydrogen or (C1-C4)alkyl (such as methyl), or R^{10} and R^{11}, or R^{12} and R^{13}, or R^{14} and R^{15}, when taken together with the nitrogen atom to which they are attached, may each suitably form a saturated heterocyclic ring, such as pyrrolidinyl or piperidinyl.

It will be appreciated that the number and nature of substituents on rings in the compounds of the invention will be selected so as to avoid sterically undesirable combinations.

In one group of compounds of formula (I) according to the invention, q is 0; R^2 is hydrogen; R^3 is selected from halogeno, (C1-C4)alkyl, (C1-C4)alkoxy and a saturated monocyclic 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur; $-NQ^1$ is a N-linked azetidinyl or pyrrolidinyl ring; Q^2 is a 5- or 6-membered heteroaromatic ring comprising one or two ring heteroatoms, which may be the same or different, selected from nitrogen and oxygen; and Q^3 is an optionally substituted unsaturated 5- or 6-membered monocyclic ring comprising one or two ring heteroatoms, which may be the same or different, selected from nitrogen, oxygen and sulfur. For example, within this group, suitable values for Q^2 are isoxazolyl and tetrazolyl (especially isoxazolyl) and suitable values for Q^3 are pyrazinyl, thiazolyl, pyrimidinyl and pyridyl (especially pyridyl, thiazolyl and pyrazinyl, more especially pyridyl).

In another group of compounds of formula (I) according to the invention, q is 0 or 1; R^1, when present, is selected from (C1-C4)alkyl and cyano; R^2 is hydrogen; R^3 is selected from halogeno, (C1-C4)alkyl, (C1-C4)alkoxy and a saturated monocyclic 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen and oxygen; $-NQ^1$ is a N-linked pyrrolidinyl ring; Q^2 is a 5-membered heteroaromatic ring comprising one or two ring heteroatoms, which may be the same or different, selected from nitrogen and oxygen; and Q^3 is an optionally substituted unsaturated 5- or 6-membered monocyclic ring comprising one or two ring heteroatoms, which may be the same or different, selected from nitrogen, oxygen and sulfur. For example, within this group, suitable values for Q^2 are isoxazolyl and suitable values for Q^3 are pyrazinyl, thiazolyl, pyrimidinyl and pyridyl (especially pyridyl, thiazolyl and pyrazinyl, more especially pyridyl).

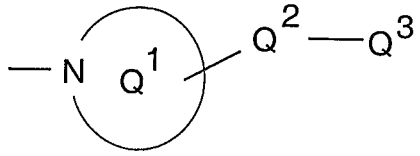
In one aspect of the invention, suitable values for the group of sub-formula (i) (which is attached to the 2-position of the pyrimidine ring of formula (I)):



(i)

include, for example, 2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl, 2-[3-(thiazol-2-yl)isoxazol-5-yl]pyrrolidin-1-yl, 2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl and 2-[3-(pyrid-2-yl)isoxazol-5-yl]azetidin-1-yl (where, for the avoidance of any doubt, it is the pyrrolidinyl-1-yl or azetidin-1-yl group that is attached to the 2-position of the pyrimidine ring in formula (I)).

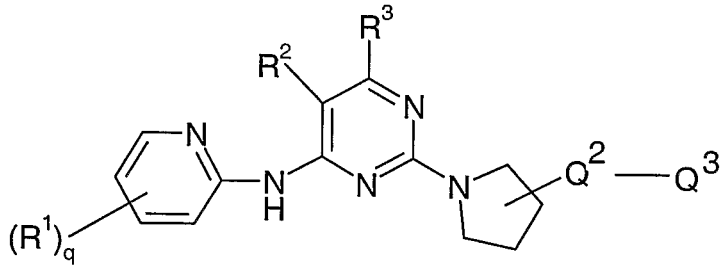
In another aspect of the invention, suitable values for the group of sub-formula (i) (which is attached to the 2-position of the pyrimidine ring of formula (I)):



(i)

include, for example, 2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl, 2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl, 2-[3-(thiazol-2-yl)isoxazol-5-yl]pyrrolidin-1-yl, 2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl, 2-[3-(2-cyanopyrid-3-yl)isoxazol-5-yl]pyrrolidin-1-yl and 2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl (where, for the avoidance of any doubt, it is the pyrrolidinyl-1-yl group that is attached to the 2-position of the pyrimidine ring in formula (I)).

A particular embodiment of the present invention is a compound of formula (Ia):



(Ia)

wherein:

R^1 is selected from cyano, or from a (C1-C6)alkyl, amino, (C1-C4)alkylamino, di-[(C1-C4)alkyl]amino, carbamoyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl or $-N(R^{1a})C(O)R^{1b}$ group, wherein R^{1a} and R^{1b} are each independently selected from hydrogen and (C1-C6)alkyl, each of which groups may be optionally substituted by one or more substituents independently selected from halogeno and (C1-C6)alkoxy;

q is 0, 1, 2 or 3;

R^2 is selected from hydrogen, halogeno and trifluoromethyl;

R^3 is selected from hydrogen, hydroxy and halogeno, or from a (C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl, (C1-C6)alkoxy, (C3-C8)cycloalkyl(C1-C6)alkoxy, (C1-C6)alkylcarbonyl, (C3-C8)cycloalkylcarbonyl, (C3-C8)cycloalkyl(C1-C6)alkylcarbonyl, (C1-C6)alkoxycarbonyl, amino, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, (C3-C8)cycloalkylamino, (C3-C8)cycloalkyl(C1-C6)alkylamino, (C1-C6)alkoxyamino, carbamoyl, (C1-C6)alkylcarbamoyl, di-[(C1-C6)alkyl]carbamoyl, $-C(O)R^{3b}$, $-OR^{3b}$, $-SR^{3b}$, $-NHR^{3b}$, $-N[(C1-C6)alkyl]R^{3b}$, $-S(O)_mR^{3a}$ or $-N(R^{3c})C(O)R^{3a}$ group, wherein m is 0, 1 or 2, R^{3a} is selected from a (C1-

C6)alkyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl or (C1-C6)alkoxy group, R^{3b} is a saturated monocyclic 4-, 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur and R^{3c} is selected from hydrogen and (C1-C6)alkyl,

or R^3 is a saturated monocyclic 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur,

or R^3 is a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur,

or R^3 is a 2,7-diazaspiro[3.5]nonane group,

each of which groups or rings within R^3 may be optionally substituted by one or more substituents independently selected from (C1-C6)alkyl, (C1-C6)alkoxy, (C1-C6)alkoxy(C1-C6)alkyl, (C1-C6)alkoxy(C1-C6)alkoxy, halogen, hydroxy, trifluoromethyl, tri-[(C1-C4)alkyl]silyl, cyano, amino, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, (C3-C8)cycloalkylamino, (C3-C6)cycloalkyl(C1-C3)alkylamino, amino(C1-C6)alkyl, (C1-C6)alkylamino(C1-C6)alkyl, di-[(C1-C6)alkyl]amino(C1-C6)alkyl, (C3-C8)cycloalkylamino(C1-C6)alkyl, (C3-C6)cycloalkyl(C1-C3)alkylamino(C1-C6)alkyl, (C1-C6)alkoxycarbonyl, carbamoyl, (C1-C6)alkylcarbamoyl, di-[(C1-C6)alkyl]carbamoyl, (C1-C6)alkylthio, (C1-C6)alkylsulfonyl, (C1-C6)alkylsulfinyl, (C1-C6)alkanoyl, an alkanoylamino group $-N(R^{3d})C(O)R^{3e}$ wherein R^{3d} is selected from hydrogen and (C1-C6)alkyl and R^{3e} is selected from a (C1-C6)alkyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl or (C1-C6)alkoxy group, or a saturated monocyclic 3-, 4-, 5-, 6- or 7-membered ring, which ring may optionally comprise one or more heteroatoms selected from nitrogen, oxygen and sulfur, any of which substituents may be optionally substituted by one or more (C1-C4)alkyl, hydroxy or cyano groups;

Q^2 is a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur, which ring is substituted by Q^3 and is optionally substituted, on any available ring atom, by one or more further substituents independently selected from (C1-C6)alkyl and (C1-C6)alkoxy (either of which (C1-C6)alkyl and (C1-C6)alkoxy substituent groups may be optionally substituted by one or more substituents independently selected from halogeno, amino, hydroxy and trifluoromethyl), halogeno, nitro, cyano, $-NR^4R^5$, carboxy, hydroxy, (C2-C6)alkenyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl, (C1-C4)alkoxycarbonyl, (C1-C4)alkylcarbonyl, (C2-C6)alkanoylamino, phenylcarbonyl, $-S(O)_p$(C1-C4)alkyl, $-C(O)NR^6R^7$ and $-SO_2NR^8R^9$,

wherein R^4, R^5, R^6, R^7, R^8 and R^9 are each independently selected from hydrogen and (C1-C6)alkyl, or R^4 and R^5, or R^6 and R^7, or R^8 and R^9, when taken together with the nitrogen atom to which they are attached, may each independently form a saturated heterocyclic ring and p is 0, 1 or 2;

Q^3 is selected from a (C1-C6)alkyl, (C3-C6)cycloalkyl or (C3-C6)cycloalkyl(C1-C6)alkyl group or a saturated or unsaturated 5- or 6-membered monocyclic ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulfur, and wherein Q^3 is optionally substituted by one or more substituents independently selected from (C1-C6)alkyl and (C1-C6)alkoxy (either of which (C1-C6)alkyl and (C1-C6)alkoxy substituent groups may be optionally substituted by one or more substituents independently selected from halogeno, amino, hydroxy and trifluoromethyl), halogeno, nitro, cyano, $-NR^{10}R^{11}$, carboxy, hydroxy, (C2-C6)alkenyl, (C3-C8)cycloalkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C2-C6)alkanoylamino, phenylcarbonyl, $-S(O)_n$(C1-C6)alkyl, $-C(O)NR^{12}R^{13}$ and $-SO_2NR^{14}R^{15}$, wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are each independently selected from hydrogen and (C1-C6)alkyl, or R^{10} and R^{11}, or R^{12} and R^{13}, or R^{14} and R^{15}, when taken together with the nitrogen atom to which they are attached, may each independently form a saturated heterocyclic ring and n is 0, 1 or 2;

and wherein any saturated monocyclic ring optionally bears 1 or 2 oxo or thioxo substituents;

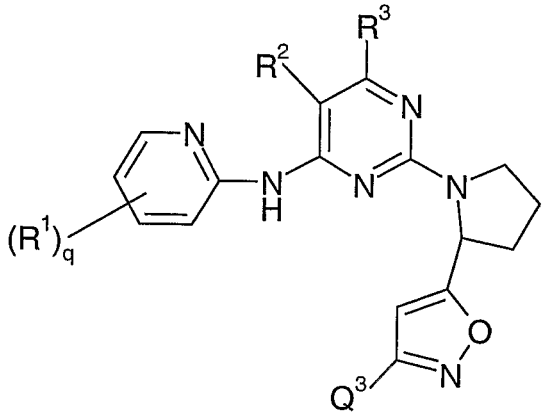
or a pharmaceutically-acceptable salt thereof.

In the compounds of formula (Ia), a suitable value for Q^2 is a 5- or 6-membered (especially 5-membered) heteroaromatic ring comprising one or two ring heteroatoms, which may be the same or different, selected from nitrogen and oxygen (such as isoxazolyl).

In the compounds of formula (Ia), a suitable value for Q^3 is an optionally substituted unsaturated 5- or 6-membered monocyclic ring comprising one or two ring heteroatoms, which may be the same or different, selected from nitrogen, oxygen and sulfur (for example, pyrazinyl, thiazolyl, pyrimidinyl and pyridyl, especially pyridyl, thiazolyl and pyrazinyl, more especially pyridyl).

In the compounds of formula (Ia), suitable substsituents for the group Q^3 include, for example (C1-C4)alkyl (such as methyl), (C1-C4)alkoxy (such as methoxy) and cyano.

Another particular embodiment of the present invention is a compound of formula (Ib):



(Ib)

wherein:

R^1 is selected from cyano, or from a (C1-C6)alkyl, amino, (C1-C4)alkylamino, di-[(C1-C4)alkyl]amino, carbamoyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl or $-N(R^{1a})C(O)R^{1b}$ group, wherein R^{1a} and R^{1b} are each independently selected from hydrogen and (C1-C6)alkyl, each of which groups may be optionally substituted by one or more substituents independently selected from halogeno and (C1-C6)alkoxy;

q is 0, 1, 2 or 3;

R^2 is selected from hydrogen, halogeno and trifluoromethyl;

R^3 is selected from hydrogen, hydroxy and halogeno, or from a (C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl, (C1-C6)alkoxy, (C3-C8)cycloalkyl(C1-C6)alkoxy, (C1-C6)alkylcarbonyl, (C3-C8)cycloalkylcarbonyl, (C3-C8)cycloalkyl(C1-C6)alkylcarbonyl, (C1-C6)alkoxycarbonyl, amino, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, (C3-C8)cycloalkylamino, (C3-C8)cycloalkyl(C1-C6)alkylamino, (C1-C6)alkoxyamino, carbamoyl, (C1-C6)alkylcarbamoyl, di-[(C1-C6)alkyl]carbamoyl, $-C(O)R^{3b}$, $-OR^{3b}$, $-SR^{3b}$, $-NHR^{3b}$, $-N[(C1-C6)alkyl]R^{3b}$, $-S(O)_mR^{3a}$ or $-N(R^{3c})C(O)R^{3a}$ group, wherein m is 0, 1 or 2, R^{3a} is selected from a (C1-C6)alkyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl or (C1-C6)alkoxy group, R^{3b} is a saturated monocyclic 4-, 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur and R^{3c} is selected from hydrogen and (C1-C6)alkyl,

or R^3 is a saturated monocyclic 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur,

or R^3 is a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur,

or R^3 is a 2,7-diazaspiro[3.5]nonane group,

each of which groups or rings within R^3 may be optionally substituted by one or more substituents independently selected from (C1-C6)alkyl, (C1-C6)alkoxy, (C1-C6)alkoxy(C1-C6)alkyl, (C1-C6)alkoxy(C1-C6)alkoxy, halogen, hydroxy, trifluoromethyl, tri-[(C1-C4)alkyl]silyl, cyano, amino, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, (C3-C8)cycloalkylamino, (C3-C6)cycloalkyl(C1-C3)alkylamino, amino(C1-C6)alkyl, (C1-C6)alkylamino(C1-C6)alkyl, di-[(C1-C6)alkyl]amino(C1-C6)alkyl, (C3-C8)cycloalkylamino(C1-C6)alkyl, (C3-C6)cycloalkyl(C1-C3)alkylamino(C1-C6)alkyl, (C1-C6)alkoxycarbonyl, carbamoyl, (C1-C6)alkylcarbamoyl, di-[(C1-C6)alkyl]carbamoyl, (C1-C6)alkylthio, (C1-C6)alkylsulfonyl, (C1-C6)alkylsulfinyl, (C1-C6)alkanoyl, an alkanoylamino group $-N(R^{3d})C(O)R^{3e}$ wherein R^{3d} is selected from hydrogen and (C1-C6)alkyl and R^{3e} is selected from a (C1-C6)alkyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl or (C1-C6)alkoxy group, or a saturated monocyclic 3-, 4-, 5-, 6- or 7-membered ring, which ring may optionally comprise one or more heteroatoms selected from nitrogen, oxygen and sulfur, any of which substituents may be optionally substituted by one or more (C1-C4)alkyl, hydroxy or cyano groups;

Q^3 is selected from a (C1-C6)alkyl, (C3-C6)cycloalkyl or (C3-C6)cycloalkyl(C1-C6)alkyl group or a saturated or unsaturated 5- or 6-membered monocyclic ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulfur, and wherein Q^3 is optionally substituted by one or more substituents independently selected from (C1-C6)alkyl and (C1-C6)alkoxy (either of which (C1-C6)alkyl and (C1-C6)alkoxy substituent groups may be optionally substituted by one or more substituents independently selected from halogeno, amino, hydroxy and trifluoromethyl), halogeno, nitro, cyano, $-NR^{10}R^{11}$, carboxy, hydroxy, (C2-C6)alkenyl, (C3-C8)cycloalkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C2-C6)alkanoylamino, phenylcarbonyl, $-S(O)_n$(C1-C6)alkyl, $-C(O)NR^{12}R^{13}$ and $-SO_2NR^{14}R^{15}$, wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are each independently selected from hydrogen and (C1-C6)alkyl, or R^{10} and R^{11}, or R^{12} and R^{13}, or R^{14} and R^{15}, when taken together with the nitrogen atom to which they are attached, may each independently form a saturated heterocyclic ring and n is 0, 1 or 2;

and wherein any saturated monocyclic ring optionally bears 1 or 2 oxo or thioxo substituents;

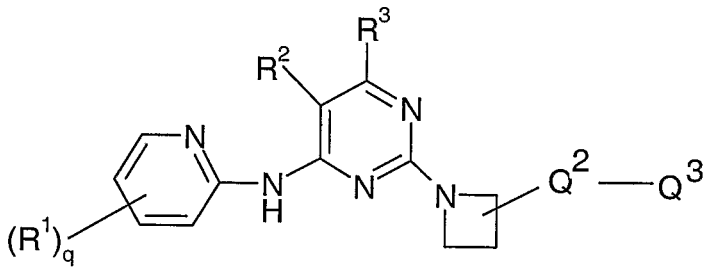
or a pharmaceutically-acceptable salt thereof.

In the compounds of formula (Ib), a suitable value for Q^3 is an optionally substituted unsaturated 5- or 6-membered monocyclic ring comprising one or two ring heteroatoms,

which may be the same or different, selected from nitrogen, oxygen and sulfur (for example, pyrazinyl, thiazolyl, pyrimidinyl and pyridyl, especially pyridyl, thiazolyl and pyrazinyl, more especially pyridyl).

In the compounds of formula (Ib), suitable substsituents for the group Q^3 include, for example (C1-C4)alkyl (such as methyl), (C1-C4)alkoxy (such as methoxy) and cyano.

Another particular embodiment of the present invention is a compound of formula (Ic):



(Ic)

wherein:

R^1 is selected from cyano, or from a (C1-C6)alkyl, amino, (C1-C4)alkylamino, di-[(C1-C4)alkyl]amino, carbamoyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl or $-N(R^{1a})C(O)R^{1b}$ group, wherein R^{1a} and R^{1b} are each independently selected from hydrogen and (C1-C6)alkyl, each of which groups may be optionally substituted by one or more substituents independently selected from halogeno and (C1-C6)alkoxy;

q is 0, 1, 2 or 3;

R^2 is selected from hydrogen, halogeno and trifluoromethyl;

R^3 is selected from hydrogen, hydroxy and halogeno, or from a (C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl, (C1-C6)alkoxy, (C3-C8)cycloalkyl(C1-C6)alkoxy, (C1-C6)alkylcarbonyl, (C3-C8)cycloalkylcarbonyl, (C3-C8)cycloalkyl(C1-C6)alkylcarbonyl, (C1-C6)alkoxycarbonyl, amino, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, (C3-C8)cycloalkylamino, (C3-C8)cycloalkyl(C1-C6)alkylamino, (C1-C6)alkoxyamino, carbamoyl, (C1-C6)alkylcarbamoyl, di-[(C1-C6)alkyl]carbamoyl, $-C(O)R^{3b}$, $-OR^{3b}$, $-SR^{3b}$, $-NHR^{3b}$, $-N[(C1-C6)alkyl]R^{3b}$, $-S(O)_mR^{3a}$ or $-N(R^{3c})C(O)R^{3a}$ group, wherein m is 0, 1 or 2, R^{3a} is selected from a (C1-C6)alkyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl or (C1-C6)alkoxy group, R^{3b} is a saturated monocyclic 4-, 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur and R^{3c} is selected from hydrogen and (C1-C6)alkyl,

or R^3 is a saturated monocyclic 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur,

or R^3 is a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur,

or R^3 is a 2,7-diazaspiro[3.5]nonane group,

each of which groups or rings within R^3 may be optionally substituted by one or more substituents independently selected from (C1-C6)alkyl, (C1-C6)alkoxy, (C1-C6)alkoxy(C1-C6)alkyl, (C1-C6)alkoxy(C1-C6)alkoxy, halogen, hydroxy, trifluoromethyl, tri-[(C1-C4)alkyl]silyl, cyano, amino, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, (C3-C8)cycloalkylamino, (C3-C6)cycloalkyl(C1-C3)alkylamino, amino(C1-C6)alkyl, (C1-C6)alkylamino(C1-C6)alkyl, di-[(C1-C6)alkyl]amino(C1-C6)alkyl, (C3-C8)cycloalkylamino(C1-C6)alkyl, (C3-C6)cycloalkyl(C1-C3)alkylamino(C1-C6)alkyl, (C1-C6)alkoxycarbonyl, carbamoyl, (C1-C6)alkylcarbamoyl, di-[(C1-C6)alkyl]carbamoyl, (C1-C6)alkylthio, (C1-C6)alkylsulfonyl, (C1-C6)alkylsulfinyl, (C1-C6)alkanoyl, an alkanoylamino group $-N(R^{3d})C(O)R^{3e}$ wherein R^{3d} is selected from hydrogen and (C1-C6)alkyl and R^{3e} is selected from a (C1-C6)alkyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl or (C1-C6)alkoxy group, or a saturated monocyclic 3-, 4-, 5-, 6- or 7-membered ring, which ring may optionally comprise one or more heteroatoms selected from nitrogen, oxygen and sulfur, any of which substituents may be optionally substituted by one or more (C1-C4)alkyl, hydroxy or cyano groups;

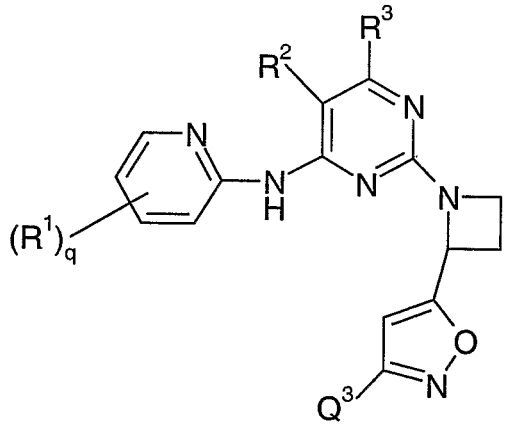
Q^2 is a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur, which ring is substituted by Q^3 and is optionally substituted, on any available ring atom, by one or more further substituents independently selected from (C1-C6)alkyl and (C1-C6)alkoxy (either of which (C1-C6)alkyl and (C1-C6)alkoxy substituent groups may be optionally substituted by one or more substituents independently selected from halogeno, amino, hydroxy and trifluoromethyl), halogeno, nitro, cyano, $-NR^4R^5$, carboxy, hydroxy, (C2-C6)alkenyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl, (C1-C4)alkoxycarbonyl, (C1-C4)alkylcarbonyl, (C2-C6)alkanoylamino, phenylcarbonyl, $-S(O)_p$(C1-C4)alkyl, $-C(O)NR^6R^7$ and $-SO_2NR^8R^9$, wherein R^4, R^5, R^6, R^7, R^8 and R^9 are each independently selected from hydrogen and (C1-C6)alkyl, or R^4 and R^5, or R^6 and R^7, or R^8 and R^9, when taken together with the nitrogen atom to which they are attached, may each independently form a saturated heterocyclic ring and p is 0, 1 or 2;

Q^3 is selected from a (C1-C6)alkyl, (C3-C6)cycloalkyl or (C3-C6)cycloalkyl(C1-C6)alkyl group or a saturated or unsaturated 5- or 6-membered monocyclic ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulfur, and wherein Q^3 is optionally substituted by one or more substituents independently selected from (C1-C6)alkyl and (C1-C6)alkoxy (either of which (C1-C6)alkyl and (C1-C6)alkoxy substituent groups may be optionally substituted by one or more substituents independently selected from halogeno, amino, hydroxy and trifluoromethyl), halogeno, nitro, cyano, $-NR^{10}R^{11}$, carboxy, hydroxy, (C2-C6)alkenyl, (C3-C8)cycloalkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C2-C6)alkanoylamino, phenylcarbonyl, $-S(O)_n$(C1-C6)alkyl, $-C(O)NR^{12}R^{13}$ and $-SO_2NR^{14}R^{15}$, wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are each independently selected from hydrogen and (C1-C6)alkyl, or R^{10} and R^{11}, or R^{12} and R^{13}, or R^{14} and R^{15}, when taken together with the nitrogen atom to which they are attached, may each independently form a saturated heterocyclic ring and n is 0, 1 or 2;

and wherein any saturated monocyclic ring optionally bears 1 or 2 oxo or thioxo substituents;

or a pharmaceutically-acceptable salt thereof.

Another particular embodiment of the present invention is a compound of formula (Id):



(Id)

wherein:

R^1 is selected from cyano, or from a (C1-C6)alkyl, amino, (C1-C4)alkylamino, di-[(C1-C4)alkyl]amino, carbamoyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl or $-N(R^{1a})C(O)R^{1b}$ group, wherein R^{1a} and R^{1b} are each independently selected from hydrogen and (C1-C6)alkyl, each of which groups may be optionally substituted by one or more substituents independently selected from halogeno and (C1-C6)alkoxy;

q is 0, 1, 2 or 3;

R^2 is selected from hydrogen, halogeno and trifluoromethyl;

R^3 is selected from hydrogen, hydroxy and halogeno, or from a (C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl, (C1-C6)alkoxy, (C3-C8)cycloalkyl(C1-C6)alkoxy, (C1-C6)alkylcarbonyl, (C3-C8)cycloalkylcarbonyl, (C3-C8)cycloalkyl(C1-C6)alkylcarbonyl, (C1-C6)alkoxycarbonyl, amino, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, (C3-C8)cycloalkylamino, (C3-C8)cycloalkyl(C1-C6)alkylamino, (C1-C6)alkoxyamino, carbamoyl, (C1-C6)alkylcarbamoyl, di-[(C1-C6)alkyl]carbamoyl, $-C(O)R^{3b}$, $-OR^{3b}$, $-SR^{3b}$, $-NHR^{3b}$, $-N[(C1-C6)alkyl]R^{3b}$, $-S(O)_mR^{3a}$ or $-N(R^{3c})C(O)R^{3a}$ group, wherein m is 0, 1 or 2, R^{3a} is selected from a (C1-C6)alkyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl or (C1-C6)alkoxy group, R^{3b} is a saturated monocyclic 4-, 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur and R^{3c} is selected from hydrogen and (C1-C6)alkyl,

or R^3 is a saturated monocyclic 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur,

or R^3 is a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur,

or R^3 is a 2,7-diazaspiro[3.5]nonane group,

each of which groups or rings within R^3 may be optionally substituted by one or more substituents independently selected from (C1-C6)alkyl, (C1-C6)alkoxy, (C1-C6)alkoxy(C1-C6)alkyl, (C1-C6)alkoxy(C1-C6)alkoxy, halogen, hydroxy, trifluoromethyl, tri-[(C1-C4)alkyl]silyl, cyano, amino, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, (C3-C8)cycloalkylamino, (C3-C6)cycloalkyl(C1-C3)alkylamino, amino(C1-C6)alkyl, (C1-C6)alkylamino(C1-C6)alkyl, di-[(C1-C6)alkyl]amino(C1-C6)alkyl, (C3-C8)cycloalkylamino(C1-C6)alkyl, (C3-C6)cycloalkyl(C1-C3)alkylamino(C1-C6)alkyl, (C1-C6)alkoxycarbonyl, carbamoyl, (C1-C6)alkylcarbamoyl, di-[(C1-C6)alkyl]carbamoyl, (C1-C6)alkylthio, (C1-C6)alkylsulfonyl, (C1-C6)alkylsulfinyl, (C1-C6)alkanoyl, an alkanoylamino group $-N(R^{3d})C(O)R^{3e}$ wherein R^{3d} is selected from hydrogen and (C1-C6)alkyl and R^{3e} is selected from a (C1-C6)alkyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl or (C1-C6)alkoxy group, or a saturated monocyclic 3-, 4-, 5-, 6- or 7-membered ring, which ring may optionally comprise one or more heteroatoms selected from nitrogen, oxygen and sulfur, any of which substituents may be optionally substituted by one or more (C1-C4)alkyl, hydroxy or cyano groups;

Q^3 is selected from a (C1-C6)alkyl, (C3-C6)cycloalkyl or (C3-C6)cycloalkyl(C1-C6)alkyl group or a saturated or unsaturated 5- or 6-membered monocyclic ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulfur, and wherein Q^3 is optionally substituted by one or more substituents independently selected from (C1-C6)alkyl and (C1-C6)alkoxy (either of which (C1-C6)alkyl and (C1-C6)alkoxy substituent groups may be optionally substituted by one or more substituents independently selected from halogeno, amino, hydroxy and trifluoromethyl), halogeno, nitro, cyano, $-NR^{10}R^{11}$, carboxy, hydroxy, (C2-C6)alkenyl, (C3-C8)cycloalkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C2-C6)alkanoylamino, phenylcarbonyl, $-S(O)_n$(C1-C6)alkyl, $-C(O)NR^{12}R^{13}$ and $-SO_2NR^{14}R^{15}$, wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are each independently selected from hydrogen and (C1-C6)alkyl, or R^{10} and R^{11}, or R^{12} and R^{13}, or R^{14} and R^{15}, when taken together with the nitrogen atom to which they are attached, may each independently form a saturated heterocyclic ring and n is 0, 1 or 2;

and wherein any saturated monocyclic ring optionally bears 1 or 2 oxo or thioxo substituents;

or a pharmaceutically-acceptable salt thereof.

Particular compounds of the invention include, for example, any one or more compounds of formula (I) selected from:

S-6-methyl-4-(2-pyridylamino)-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine;

S-6-chloro-4-(2-pyridylamino)-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine;

S-6-morpholino-4-(2-pyridylamino)-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine;

S-6-methoxy-4-(2-pyridylamino)-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine;

S-6-methyl-4-(2-pyridylamino)-2-{2-[3-(thiazol-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine; and

S-6-methyl-4-(2-pyridylamino)-2-{2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine;

and pharmaceutically-acceptable salts thereof.

In another aspect of the invention, particular compounds of the invention include, for example, any one or more compounds of formula (I) selected from:

S-6-methyl-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-chloro-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-morpholino-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methoxy-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(thiazol-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-ethyl-2-{2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(2-cyanopyrid-3-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-ethyl-2-{2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(4-methylpyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(5-methylpyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(5-cyanopyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(4-cyanopyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(5-cyanopyrid-2-ylamino)pyrimidine;

S-6-methoxy-2-{2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methoxy-2-{2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine; and

S-6-methoxy-2-{2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

and pharmaceutically-acceptable salts thereof.

In another aspect of the invention, particular compounds of the invention include, for example, any one or more compounds of formula (I) selected from:

S-6-methyl-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-morpholino-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(thiazol-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-ethyl-2-{2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(2-cyanopyrid-3-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-ethyl-2-{2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(4-methylpyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(5-methylpyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(5-cyanopyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(4-cyanopyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(5-cyanopyrid-2-ylamino)pyrimidine;

S-6-methoxy-2-{2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

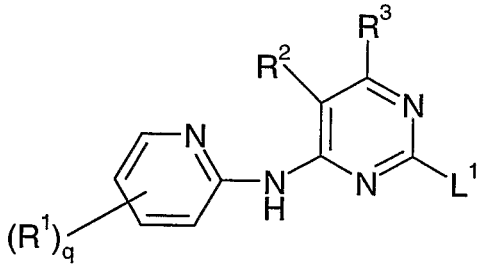
S-6-methoxy-2-{2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine; and

S-6-methoxy-2-{2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

and pharmaceutically-acceptable salts thereof.

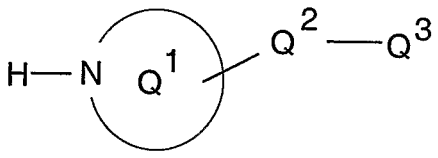
A compound of formula (I), or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a compound of formula (I) are provided as a further feature of the invention and are illustrated by the following representative process variants in which, unless otherwise stated, $-NQ^1$, Q^2, Q^3, q, R^1, R^2 and R^3 have any of the meanings defined hereinbefore. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and within the accompanying Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

Process (a) the reaction, conveniently in the presence of a suitable base, of a compound of formula (II):



(II)

wherein L^1 represents a suitable displaceable group and q, R^1, R^2 and R^3 are as defined in formula (I) except that any functional group is protected if necessary, with a compound of formula (III):



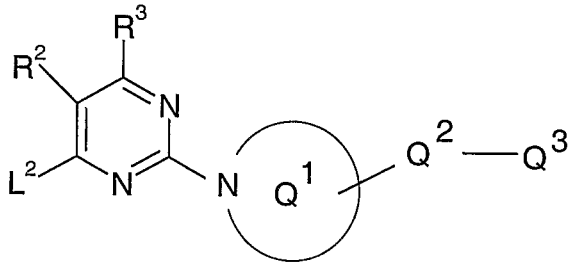
(III)

wherein $-NQ^1$, Q^2 and Q^3 are as defined in formula (I) except that any functional

group is protected if necessary;

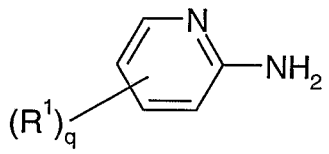
or

Process (b) the reaction, conveniently in the presence of a suitable acid, of a compound of formula (IV):



(IV)

wherein L^2 is a suitable displaceable group and R^2, R^3, $-NQ^1$, Q^2 and Q^3 are as defined in formula (I) except that any functional group is protected if necessary, with an amino-pyridine of formula (V):

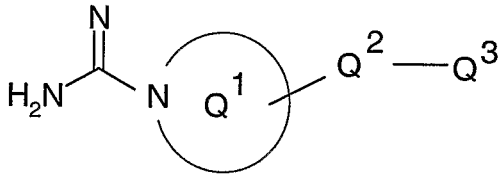


(V)

wherein q and R^1 are as defined in formula (I) except that any functional group is protected if necessary;

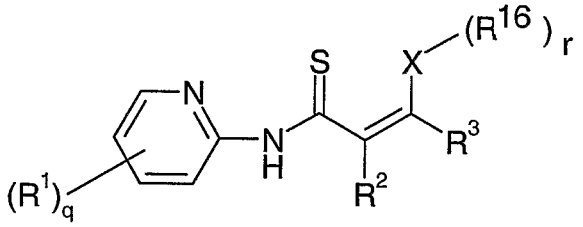
or

Process (c) the reaction, conveniently in the presence of a suitable base, of a compound of formula (VI):



(VI)

wherein $-NQ^1$, Q^2 and Q^3 are as defined in formula (I) except that any functional group is protected if necessary, with a compound of formula (VII):

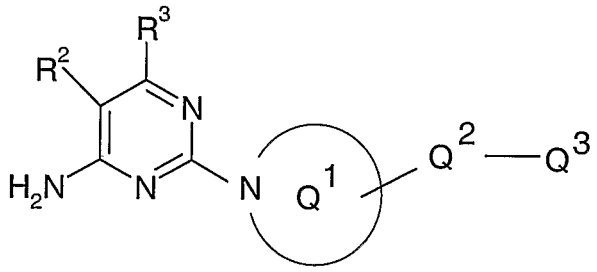


(VII)

wherein X represents an oxygen atom and r is 1 or X represents a nitrogen atom and r is 2, R^{16} is a (C1-C6)alkyl group and q, R^1, R^2 and R^3 are as defined in formula (I) except that any functional group is protected if necessary;

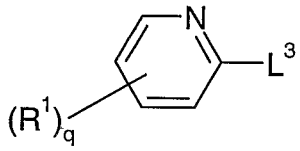
or

Process (d) the reaction of a compound of formula (VIII):



(VIII)

wherein $-NQ^1$, Q^2, Q^3, R^2 and R^3 are as defined in formula (I) except that any functional group is protected if necessary, with a compound of formula (IX):

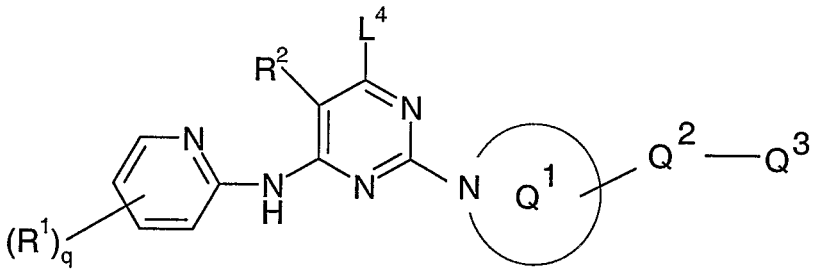


(IX)

wherein L^3 is a suitable displaceable group and q and R^1 are as defined in formula (I) except that any functional group is protected if necessary;

or

Process (e) for compounds of formula (I) wherein R^3 is a (C1-C6)alkoxy, amino, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, $-OR^{3b}$, $-SR^{3b}$, $-NHR^{3b}$, $-N[(C1-C6)alkyl]R^{3b}$ or $-S(O)_mR^{3a}$ group wherein m is 0 and R^{3a} and R^{3b} are as defined above (and the group R^3 is optionally substituted by at least one group as defined above), the reaction, conveniently in the presence of a suitable base, of a compound of formula (X):



(X)

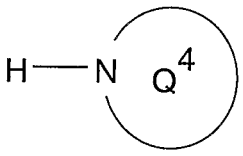
wherein L^4 is a suitable displaceable group and q, R^1, R^2, $-NQ^1$, Q^2 and Q^3 are as defined in formula (I) except that any functional group is protected if necessary, with a compound of formula:

H-Xa

wherein Xa represents OR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, OR^{3b}, SR^{3b}, NHR^{3b}, $N[(C1-C6)alkyl]R^{3b}$ and SR^{3a}, wherein R^{17} is an, optionally substituted, (C1-C6)alkyl group and R^{3a}

and R^{3b} are each as defined above except that any functional group is protected if necessary; or

Process (f) for compounds of formula (I) wherein R^3 is (i) an, optionally substituted, saturated monocyclic 5- or 6-membered heterocyclic ring comprising at least one ring nitrogen and, optionally, one or more additional heteroatoms selected from nitrogen, oxygen and sulfur, or (ii) an optionally substituted 2,7-diazaspiro[3.5]nonane group, the reaction, conveniently in the presence of a suitable base, of a compound of formula (X) as defined above, with (i) a compound of formula (Xb):



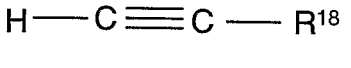
(Xb)

wherein Q^4 is a saturated monocyclic 5- or 6-membered heterocyclic ring optionally comprising one or more heteroatoms selected from nitrogen, oxygen and sulfur in addition to the nitrogen atom shown above, which ring is optionally substituted by at least one group as defined above, or

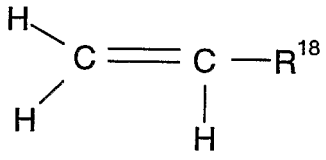
with (ii) an optionally substituted 2,7-diazaspiro[3.5]nonane;

or

Process (g) for compounds of formula (I) wherein R^3 is a (C2-C6)alkenyl or (C2-C6)alkynyl group, and the group R^3 is optionally substituted by at least one group as defined above, the reaction, conveniently in the presence of a suitable base and a suitable catalyst, of a compound of formula (X) as defined above, with a compound of formula (Xc) or of formula (Xc'):



(Xc)



(Xc')

wherein R^{18} is selected from hydrogen and an, optionally substituted, (1-4C)alkyl or (C1-C4)alkoxycarbonyl group;

or

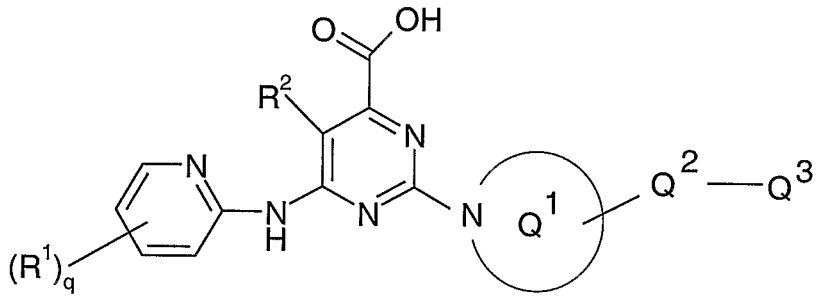
Process (h) for compounds of formula (I) wherein R^3 is attached to the pyrimidine ring through a carbon atom, the reaction, conveniently in the presence of a suitable catalyst, of a

compound of formula (X) as defined above, with a compound of the formula:

$M\text{-}R^3$

wherein R^3 is appropriately selected from the R^3 groups as defined above and M is a metallic group, such as ZnBr, $B(OH)_2$, CuCN or $SnBu_3$; or

Process (i) for compounds of formula (I) wherein R^3 is a (C1-C6)alkoxycarbonyl group (and the group R^3 is optionally substituted by at least one group as defined above), the reaction, conveniently in the presence of a suitable acid, of a compound of formula (XI):



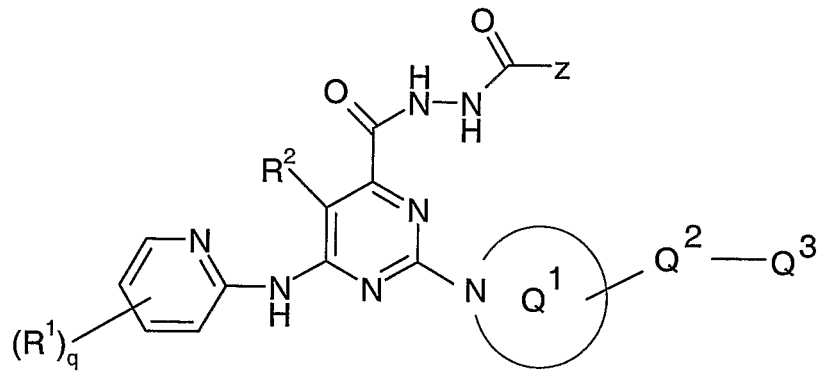
(XI)

wherein q, R^1, R^2, $-NQ^1$, Q^2 and Q^3 are as defined in formula (I) except that any functional group is protected if necessary, with a compound of formula:

H-O-(C1-C6)alkyl

wherein the (C1-C6)alkyl group is optionally substituted by at least one group as defined above as a substituent for R^3 and any functional group is protected if necessary; or

Process (j) for compounds of formula (I) wherein R^3 is a 5-membered heteroaromatic ring comprising at least one heteroatom selected from nitrogen, oxygen and sulfur (and the group R^3 is optionally substituted by at least one group as defined above), an internal condensation reaction using an appropriate starting material and a suitable dehydrating agent. For example, for compounds of formula (I) wherein R^3 is a 1,3,4-oxadiazole group, the reaction of a compound of formula (XII):

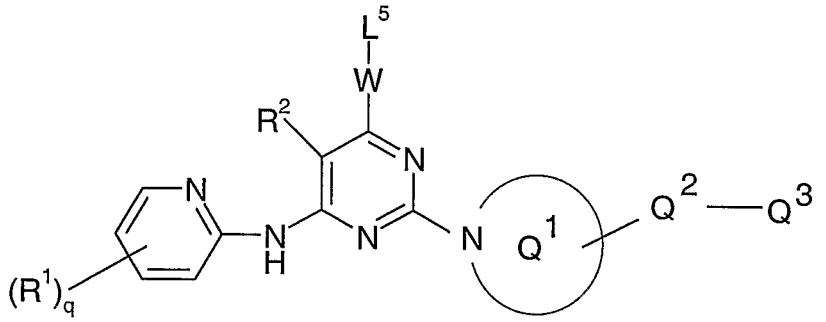


(XII)

wherein Z represents any suitable substituent for R^3 as defined above and q, R^1, R^2, $-NQ^1$, Q^2 and Q^3 are as defined in formula (I) except that any functional group is protected if

necessary, with a suitable dehydrating agent, such as (methoxycarbonylsulfamoyl)triethylammonium hydroxide; or

Process (k) for compounds of formula (I) wherein R^3 is a (C1-C6)alkyl, (C3-C6)alkenyl, (C3-C6)alkynyl or (C1-C6)alkoxy group substituted by at least one group as defined above, reacting a compound of formula (XIII):



(XIII)

wherein L^5 is a suitable displaceable group, W is an optionally substituted (C1-C6)alkyl, (C3-C6)alkenyl, (C3-C6)alkynyl or (C1-C6)alkoxy group and q, R^1, R^2, $-NQ^1$, Q^2 and Q^3 are as defined in formula (I) except that any functional group is protected if necessary, with a compound of formula H-Xa, (Xb), (Xc), (Xc') or M-R^3 as defined above;

and optionally after process (a), (b), (c), (d), (e), (f), (g), (h), (i), (j) or (k) 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.

Process (a)

Reaction Conditions for Process (a)

A suitable displaceable group L^1 in the compound of formula (II) is for example a halogeno or a sulfonyloxy group, for example a fluoro, chloro, methylsulfonyloxy or toluene-4-sulfonyloxy group. A particular group L^1 is fluoro, chloro or methylsulfonyloxy.

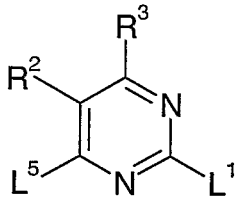
Process (a) conveniently may be carried out in the presence of a suitable base and/or in the presence of a suitable Lewis acid. A suitable base is, for example, an organic amine base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, di-isopropylethylamine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate, such as sodium carbonate, potassium carbonate, cesium carbonate or calcium carbonate, or, for example, an alkali metal hydride, such as sodium hydride. A particular base is an organic amine base, for example N,N-diisopropylethylamine. A suitable Lewis acid is zinc acetate.

Process (a) may conveniently be carried out in the presence of a suitable inert solvent or diluent for example a ketone such as acetone or an alcohol such as ethanol, butanol, isopropanol or n-hexanol or an aromatic hydrocarbon such as xylene, toluene or *N*-methyl pyrrolid-2-one and at a temperature in the range from 0°C to reflux, particularly reflux.

Process (a) may alternatively conveniently be carried out under standard Buchwald conditions (see, for example, *J. Am. Chem. Soc.*, **118**, 7215; *J. Am. Chem. Soc.*, **119**, 8451; *J. Org. Chem.*, **62**, 1568 and 6066). For example, process (a) may conveniently be carried out in the presence of palladium acetate or tris(dibenzylideneacetone)dipalladium(0), in a suitable inert solvent or diluent for example an ether such as dioxane or an aromatic solvent such as toluene, benzene or xylene, in the presence of a suitable base, for example an inorganic base such as cesium carbonate or an organic base such as potassium-*t*-butoxide and in the presence of a suitable ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl or 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene and at a temperature in the range from 25 to 80°C.

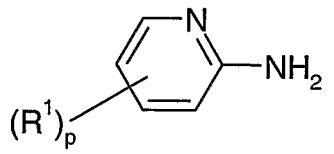
Starting Materials for Process (a)

A compound of formula (II) may be obtained by conventional procedures. For example, a compound of formula (II) may be obtained by the reaction, conveniently in the presence of a suitable base, of a pyrimidine of formula (IIa):



(IIa)

wherein L^5 is a suitable displaceable group and L^1, R^2 and R^3 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an amino-pyridine of formula (V):



(V)

wherein q and R^1 have any of the meanings defined hereinbefore except that any functional group is protected if necessary.

A suitable displaceable group L^5 in the compound of formula (IIa) is, for example, a halogeno or a sulfonyloxy group, for example a fluoro, chloro, methylsulfonyloxy or toluene-4-sulfonyloxy group. A particular group L^5 is chloro.

A suitable base for the reaction of a pyrimidine of formula (IIa) and an amino-pyridine of formula (V) includes, for example, an alkali or alkaline earth metal carbonate, such as sodium carbonate, potassium carbonate, cesium carbonate or calcium carbonate or an organic amine base such as di-isopropylethylamine.

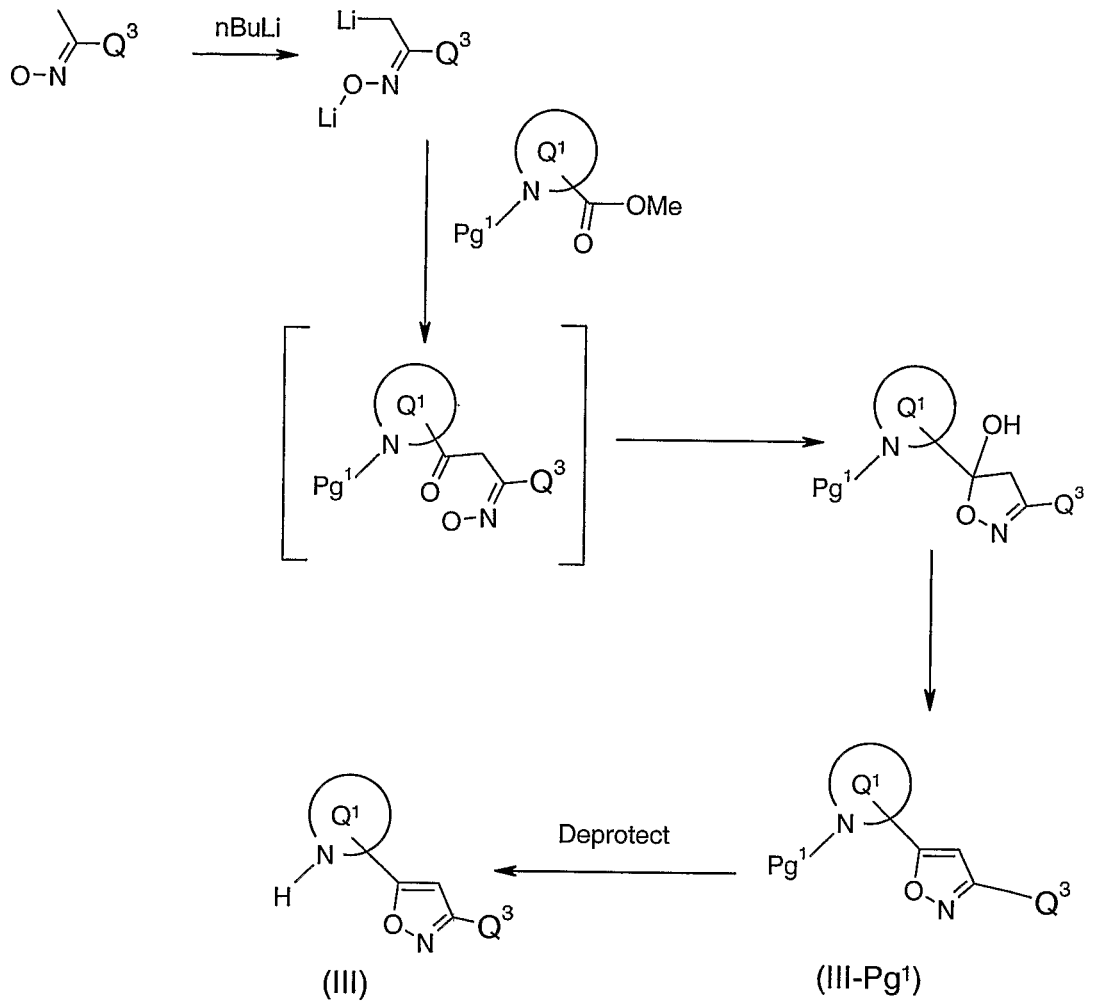
Alternatively, the reaction may conveniently be carried out in the presence of sodium bis(trimethylsilyl)amide or lithium bis(trimethylsilyl)amide.

The reaction may conveniently be carried out in the presence of a suitable inert solvent or diluent for example a ketone such as acetone or an alcohol such as ethanol, butanol or n-hexanol or an aromatic hydrocarbon such as toluene or *N*-methyl pyrrolid-2-one. The reaction is conveniently carried out at a temperature in the range of, for example, 10 to 150°C, particularly at room temperature.

Alternatively, the reaction of a pyrimidine of formula (IIa) and an amino-pyridine of formula (V) may conveniently be carried out under standard Buchwald conditions, as discussed above.

Pyrimidines of formula (IIa) and amino-pyridines of formula (V) are commercially available compounds or they are known in the literature, or they can be prepared by standard processes known in the art.

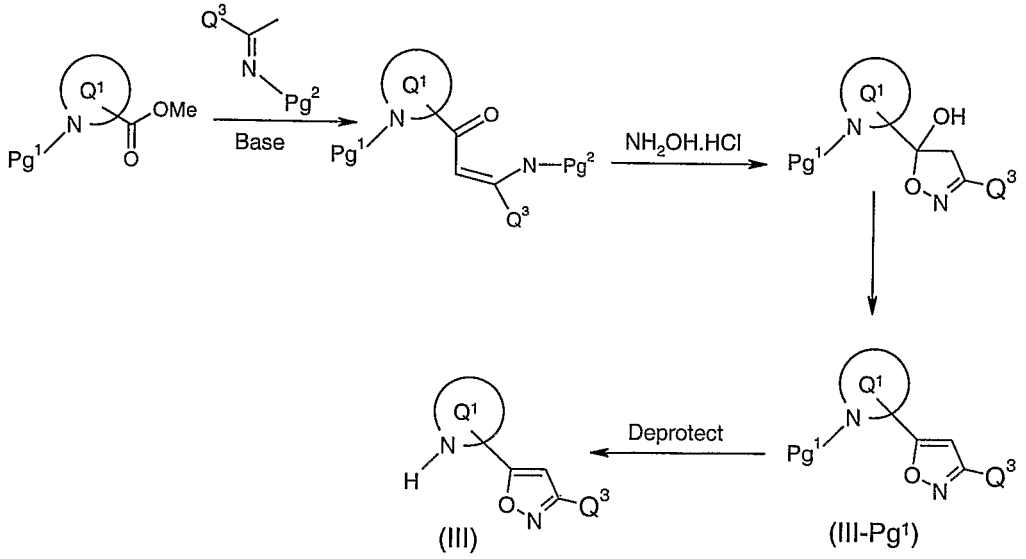
A compound of formula (III) may be obtained by conventional procedures. For example, when Q^2 is isoxazole, a compound of formula (III) may be obtained as illustrated in *Reaction Scheme 1*:



Reaction Scheme 1

In *Reaction Scheme 1*, Pg^1 is a suitable protecting group, such as, for example, tert-butoxycarbonyl. The groups $-NQ^1$ and Q^3 are as previously defined. Q^3 may be, for example, pyridyl (such as pyrid-2-yl).

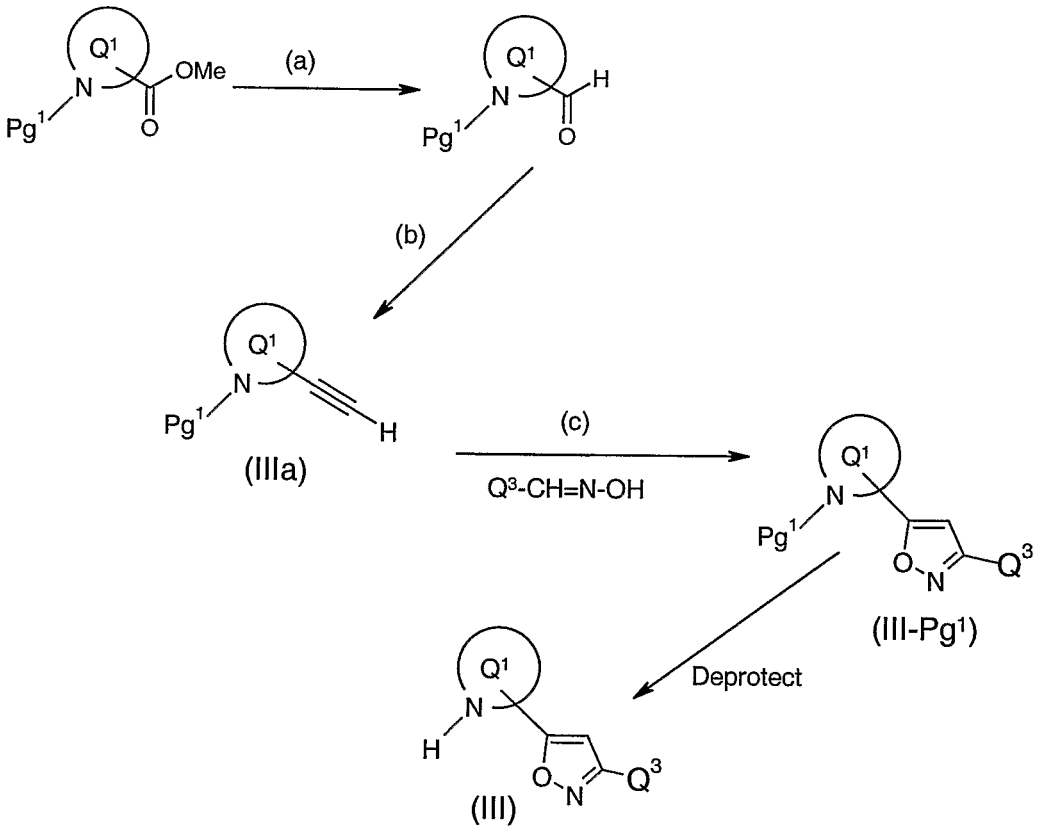
Alternatively, for example, when Q^2 is isoxazole, a compound of formula (III) may be obtained as illustrated in *Reaction Scheme 2*:



Reaction Scheme 2

In *Reaction Scheme 2*, Pg^1 is a suitable protecting group as described above. Similarly, Pg^2 is a suitable protecting group such as, for example, cyclohexyl. The groups $-NQ^1$ and Q^3 are as previously defined.

Alternatively, for example, when Q^2 is isoxazole, a compound of formula (III) may be obtained as illustrated in *Reaction Scheme 3*:



Reaction Scheme 3

In *Reaction Scheme 3*, Pg^1 is a suitable protecting group as described above. The groups $-NQ^1$ and Q^3 are as previously defined.

In *Reaction Scheme 3*, step (a) may conveniently be effected by a suitable reducing agent, such as diisobutylaluminium hydride. Step (a) may conveniently be carried out in the presence of a suitable inert solvent or diluent, for example an ether or aromatic hydrocarbon such as toluene or a chlorinated hydrocarbon such as dichloromethane, and at a temperature in the range of, for example, from -78°C to 25°C.

Step (b) may conveniently be carried out by reaction with dimethyl (1-diazo-2-oxopropyl) phosphonate in the presence of a suitable inert solvent or diluent for example a chlorinated hydrocarbon such as dichloromethane and at a temperature in the range of, for example, from -20°C to 50°C.

Alternatively, step (b) may be conducted by reaction with carbon tetrabromide, zinc and triphenylphosphine to provide a 2-(dibromoethenyl) intermediate, in the presence of a suitable inert solvent or diluent for example a chlorinated hydrocarbon such as dichloromethane and at a temperature in the range of, for example, -20 to 50°C. The conversion of the 2-(dibromoethenyl) intermediate to the 2-ethynyl intermediate may then be conducted by reaction with n-butyl lithium in the presence of a suitable inert solvent or diluent for example an ether such as tetrahydrofuran and at a temperature in the range of, for example, -70 to 0°C.

Step (c) may conveniently be effected by treatment with a suitable chlorinating agent, such as N-chlorosuccinimide, to give an α-chloroaldyde oxime intermediate and then a suitable base, such as triethylamine, to give a nitrile oxide intermediate which takes part in a 3+2 cycloaddition reaction. Alternatively, the oxime (Q^3-CH=N-OH) may be directly transformed into the nitrile oxide intermediate by treatment with sodium hypochlorite. Such reactions may conveniently be carried out in the presence of a suitable inert solvent or diluent, for example a chlorinated hydrocarbon such as dichloromethane, and at a temperature in the range of, for example, from -20°C to 50°C.

As the skilled person would appreciate, the intermediate (IIIa) may alternatively be obtained from an appropriate azetidinone or pyrrolidinone compound using standard conditions. Suitable conditions for such a transformation include reaction with a suitable reducing agent, such as borane, diisobutylaluminium hydride or lithium aluminium hydride in the presence of a suitable inert solvent or diluent (for example an ether or aromatic

hydrocarbon such as toluene or a chlorinated hydrocarbon such as dichloromethane) and at a temperature in the range of, for example, from -50°C to 100°C.

In each of *Reaction Schemes 1, 2 and 3*, the protecting group may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the particular protecting group used.

Process (b)

Reaction Conditions for Process (b)

A suitable displaceable group L^2 in a compound of formula (IV) is, for example, halogeno or a sulfonyloxy group, for example fluoro, chloro, methanesulfonyloxy or toluene-4-sulfonyloxy.

Process (b) is conveniently carried out in the presence of a suitable acid. A suitable acid is, for example, an inorganic acid such as anhydrous hydrogen chloride.

Process (b) may conveniently be carried out in the presence of a suitable inert solvent or diluent for example a ketone such as acetone or an alcohol such as ethanol, butanol or n-hexanol or an aromatic hydrocarbon such as toluene or *N*-methyl pyrrolid-2-one and at a temperature in the range from 0°C to reflux, particularly reflux.

Process (b) may alternatively conveniently be carried out under standard Buchwald conditions as discussed above for process (a).

Starting Materials for Process (b)

A compound of formula (IV) may be prepared using conventional methods, for example as discussed above.

Amino-pyridines of formula (V) are commercially available compounds or they are known in the literature, or they can be prepared by standard processes known in the art.

Process (c)

Reaction Conditions for Process (c)

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

Starting Materials for Process (c)

Compounds of the formulae (VI) and (VII) are commercially available compounds or they are known in the literature, or they can be prepared by standard processes known in the art.

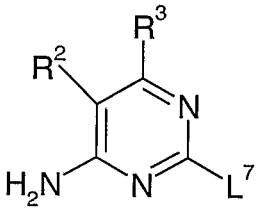
Process (d)

Reaction Conditions for Process (d)

The reaction of process (d) is conveniently carried out using analogous conditions to those described above for process (a). In particular, the reaction of process (d) may conveniently be carried out under standard Buchwald conditions, as discussed above.

Starting Materials for Process (d)

A compound of formula (VIII) may be obtained by conventional procedures. For example, a compound of formula (VIII) may be obtained by the reaction, conveniently in the presence of a suitable base, of a pyrimidine of formula (VIIIa):



(VIIIa)

wherein L^7 is a suitable displaceable group and R^2 and R^3 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with compound of formula (III) as defined hereinbefore.

A suitable displaceable group L^7 in the compound of formula (VIIIa) is, for example, a halogeno or a sulfonyloxy group, for example a fluoro, chloro, methylsulfonyloxy or toluene-4-sulfonyloxy group. A particular group L^7 is chloro.

A suitable base for the reaction of a pyrimidine of formula (VIIIa) and a compound of formula (III) includes, for example, an alkali or alkaline earth metal carbonate, for example sodium carbonate, potassium carbonate, cesium carbonate or calcium carbonate.

The reaction may conveniently be carried out in the presence of a suitable inert solvent or diluent for example a ketone such as acetone or an alcohol such as ethanol, butanol or n-hexanol or an aromatic hydrocarbon such as toluene or *N*-methyl pyrrolid-2-one. The reaction is conveniently carried out at a temperature in the range of, for example, 10 to 150°C, particularly at room temperature.

Pyrimidines of formula (VIIa) are commercially available compounds or they are known in the literature, or they can be prepared by standard processes known in the art.

A compound of formula (III) may be obtained by conventional procedures, for example as discussed above.

Process (e)

Reaction Conditions for Process (e)

A suitable displaceable group L^4 in a compound of formula (X) is, for example, halogeno or a sulfonyloxy group, for example fluoro, chloro, methanesulfonyloxy or toluene-4-sulfonyloxy.

Process (e) is conveniently carried out in the presence of a suitable base. A suitable base is, for example, sodium hydride or an organic amine base such as N,N-diisopropylethylamine. Another suitable base is an alkali metal alkoxide, for example sodium methoxide or sodium ethoxide.

Process (e) is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a ketone such as acetone, or an alcohol such as methanol, ethanol, butanol or n-hexanol, an ether such as tetrahydrofuran or an aromatic hydrocarbon such as toluene or *N*-methyl pyrrolid-2-one, optionally in the presence of a suitable base.

Process (e) is conveniently carried out at a temperature in the range from 0°C to reflux, particularly reflux. Conveniently, process (e) may also be performed by heating the reactants in a sealed vessel using a suitable heating apparatus such as a microwave heater.

Starting Materials for Process (e)

A compound of formula (X) may be prepared using conventional methods, for example as discussed above.

Compounds of the formula H-Xa are commercially available compounds or they are known in the literature, or they can be prepared by standard processes known in the art.

Process (f)

Reaction Conditions for Process (f)

The reaction of process (f) is conveniently carried out using analogous conditions to those described above for process (e).

Starting Materials for Process (f)

A compound of formula (X) may be prepared using conventional methods, for example as discussed above.

Compounds of the formula Xb are commercially available compounds or they are known in the literature, or they can be prepared by standard processes known in the art. 2,7-diazaspiro[3.5]nonane (and substituted derivatives thereof) is a commercially available compound.

Process (g)

Reaction Conditions for Process (g)

Process (g) is conveniently carried out in the presence of a suitable base. A suitable base is, for example, an organic amine base, such as for example triethylamine or N,N-diisopropylethylamine.

Process (g) is conveniently carried out in the presence of a suitable catalyst. A suitable catalyst is, for example, copper iodide / palladium (II) chloride-bis(triphenyl)phosphine.

Process (g) is conveniently carried out in the presence of a suitable inert solvent or diluent for example acetonitrile, THF or dioxane and at a temperature in the range from 0°C to reflux, particularly reflux. Conveniently, process (g) may also be performed by heating the reactants in a sealed vessel using a suitable heating apparatus such as a microwave heater.

Starting Materials for Process (g)

A compound of formula (X) may be prepared using conventional methods, for example as discussed above.

Compounds of the formula Xc and Xc' are commercially available compounds or they are known in the literature, or they can be prepared by standard processes known in the art.

Process (h)

Reaction Conditions for Process (h)

Process (h) is conveniently carried out in the presence of a suitable catalyst. A suitable catalyst is, for example, a palladium (0) catalyst, such as for example tetrakis(triphenyl)phosphine palladium(0). As a person skilled in the art would appreciate, the palladium (0) catalyst may be prepared *in situ*.

Process (h) is conveniently carried out in the presence of a suitable inert solvent or diluent for example THF or dioxane and at a temperature in the range from 0°C to reflux, particularly reflux.

Starting Materials for Process (h)

A compound of formula (X) may be prepared using conventional methods, for example as discussed above.

Compounds of the formula M-R^3 are commercially available compounds or they are known in the literature, or they can be prepared by standard processes known in the art.

Process (i)

Reaction Conditions for Process (i)

Process (i) is conveniently carried out in the presence of a suitable acid. A suitable acid is, for example, concentrated sulfuric acid.

Process (i) is conveniently carried out in the absence of an inert solvent or diluent and at a temperature in the range from room temperature to reflux, particularly reflux.

Starting Materials for Process (i)

A compound of formula (XI) may be prepared using conventional methods, for example as discussed above.

Compounds of the formula H-O-(C1-C6)alkyl are commercially available compounds or they are known in the literature, or they can be prepared by standard processes known in the art.

Process (j)

Reaction Conditions for Process (j)

Process (j) is conveniently carried out in the presence of a suitable inert solvent or diluent, such as for example dichloromethane, THF or dioxane. Process (j) is conveniently carried out at a temperature in the range from 0°C to reflux, particularly reflux.

Starting Materials for Process (j)

A compound of formula (XII) may be prepared using conventional methods, for example as discussed above.

Suitable dehydrating agents are commercially available compounds or they are known in the literature, or they can be prepared by standard processes known in the art.

Process (k)

Reaction Conditions for Process (k)

A suitable displaceable group L^5 in a compound of formula (XIII) is, for example, halogeno or a sulfonyloxy group, for example fluoro, chloro, methanesulfonyloxy or toluene-4-sulfonyloxy.

The reaction of process (k) is conveniently carried out using analogous conditions to those described above for process (e).

Starting Materials for Process (k)

A compound of formula (XIII) may be prepared using conventional methods, for example as discussed above.

Compounds of the formula H-Xa, (Xb), (Xc), (Xc') or M-R^3 are commercially available compounds or they are known in the literature, or they can be prepared by standard processes known in the art.

As stated above, compounds of formulae (II), (III), (IV), (V), (VI), (VII), (VIII), (X), HXa, (Xb), (Xc), (Xc') and M-R^3 are either commercially available, are known in the literature or may be prepared using known techniques. For example, these compounds may be prepared by analogous processes to those described in WO 03/048133. Examples of preparation methods for certain of these compounds are given hereinafter in the examples.

It will be appreciated that compounds of formula (I) can be converted into further compounds of formula (I) using standard procedures conventional in the art, for example by means of conventional substitution reactions or of conventional functional group modifications either prior to or immediately following the processes mentioned above, and such procedures are included in the process aspect of the invention.

Examples of the types of conversion reactions that may be used include introduction of a substituent by means of an aromatic substitution reaction or of a nucleophilic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art.

Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid; the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of nucleophilic substitution reactions include the introduction of an alkoxy group or of an alkylamino group, a dialkyamino group or a N-containing heterocycle using standard conditions. Particular examples of reduction reactions include the reduction of a carbonyl group to a hydroxy group with sodium borohydride or 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; and particular examples of oxidation reactions include oxidation of alkylthio to alkylsulfinyl or alkylsulfonyl. Other conversion reactions that may be used include the acid catalysed esterification of carboxylic acids with alcohols.

An example of a suitable conversion reaction is the conversion of a compound of formula (I) wherein R^3 is a (C1-C6)alkenyl group to a compound of formula (I) wherein R^3 is

a (C1-C6)alkyl group substituted by a di-[(C1-C6)alkyl]amino group or by a saturated monocyclic 4- to 7-membered ring, which ring comprises nitrogen and one or more heteroatoms independently selected from nitrogen, oxygen and sulfur. Such a conversion may be achieved using standard procedures, for example by conversion of the alkenyl group to a dihydroxyalkyl group with osmium tetroxide, oxidation to the corresponding ketone with a suitable oxidising agent (for example sodium periodate) and conversion of the ketone group to the desired substituent as defined above by reaction with the appropriate amine in the presence of a suitable reducing agent (for example sodium cyanoborohydride).

Another example of a suitable conversion reaction is the conversion of a compound of formula (I) wherein R^3 is an optionally substituted (C1-C6)alkoxycarbonyl group to a compound of formula (I) wherein R^3 is an optionally substituted carbamoyl, (C1-C6)alkylcarbamoyl or di-[(C1-C6)alkyl]carbamoyl group or an optionally substituted –C(O)R^{3b} group, wherein R^{3b} is as defined above. Such a conversion may be achieved using standard procedures, for example by reaction of the compound of formula (I) wherein R^3 is an optionally substituted (C1-C6)alkoxycarbonyl group with ammonia, with an optionally substituted primary, secondary or tertiary amine or with an optionally substituted H-R^{3b} group. As the skilled person would appreciate, this conversion could be conducted starting from the carboxylic acid and preparing an activated ester, for example using 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methyl-morpholinium chloride, which may then be reacted with the necessary amine.

Another example of a suitable conversion reaction is the conversion of a compound of formula (I) wherein R^3 is a (C1-C6)alkoxycarbonyl group to a compound of formula (I) wherein R^3 is a hydroxy-(C1-C6)alkyl group. Such a conversion may be achieved using standard procedures, for example by reduction using lithium borohydride or lithium aluminium hydride.

It will be appreciated that the preparation of compounds of formula (I) may involve, at various stages, the addition and removal of one or more protecting groups. The protecting groups used in the processes above may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such

methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied preferably has 1 to 4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned are, of course, within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1 to 20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1 to 12C)alkyl groups (for example isopropyl, and tert-butyl); lower alkoxy- lower alkyl groups (for example methoxymethyl, ethoxymethyl and isobutoxymethyl); lower acyloxy-lower alkyl groups, (for example acetoxymethyl, propionyloxymethyl, butyryloxymethyl and pivaloyloxymethyl); lower alkoxycarbonyloxy-lower alkyl groups (for example 1-methoxycarbonyloxyethyl and 1-ethoxycarbonyloxyethyl); aryl-lower alkyl groups (for example benzyl, 4-methoxybenzyl, 2-nitrobenzyl, 4-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for example trimethylsilyl and tert-butyldimethylsilyl); tri(lower alkyl)silyl-lower alkyl groups (for example trimethylsilylethyl); and (2-6C)alkenyl groups (for example allyl). Methods particularly appropriate for the removal of carboxy protecting groups include for example acid-, base-, metal- or enzymically-catalysed cleavage.

Examples of hydroxy protecting groups include lower alkyl groups (for example tert-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxycarbonyl groups (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); tri(lower alkyl)silyl (for example trimethylsilyl and tert-butyldimethylsilyl) and aryl-lower alkyl (for example benzyl) groups.

Examples of amino protecting groups include formyl, aryl-lower alkyl groups (for example benzyl and substituted benzyl, 4-methoxybenzyl, 2-nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-4-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl (for example

allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); lower alkanoyloxyalkyl groups (for example pivaloyloxymethyl); trialkylsilyl (for example trimethylsilyl and tert-butyldimethylsilyl); alkylidene (for example methylidene) and benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as 2-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as 2-nitrobenzyloxycarbonyl. For example a tert butoxycarbonyl protecting group may be removed from an amino group by an acid catalysed hydrolysis using trifluoroacetic acid.

The reader is referred to Advanced Organic Chemistry, 4th Edition, by J. March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents and to Protective Groups in Organic Synthesis, 2nd Edition, by T. Green *et al.*, also published by John Wiley & Son, for general guidance on protecting groups.

When a pharmaceutically-acceptable salt of a compound of formula (I) is required, for example an acid-addition salt, it may be obtained by, for example, reaction of said compound with a suitable acid using a conventional procedure. When it is desired to obtain the free base from a salt of the compound of formula (I), a solution of the salt may be treated with a suitable base, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide.

As mentioned hereinbefore some of the compounds according to the present invention may contain one or more chiral centers and may therefore exist as stereoisomers. Stereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The enantiomers may be isolated by separation of a racemate for example by fractional crystallisation, resolution or HPLC. The diastereoisomers may be isolated by separation by virtue of the different physical properties of the diastereoisomers, for example, by fractional crystallisation, HPLC or flash chromatography. Alternatively particular stereoisomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent. When a specific stereoisomer is isolated it is suitably isolated substantially

free for other stereoisomers, for example containing less than 20%, particularly less than 10% and more particularly less than 5% by weight of other stereoisomers.

In the section above relating to the preparation of the compounds of formula (I), the expression "inert solvent" refers to a solvent which does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in different order, and/or the individual reactions may be performed at different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

Certain intermediates used in the processes described above are novel and form a further feature of the present invention. Accordingly there is provided a compound selected from a compound the formulae (III) and (III-Pg^1) as hereinbefore defined, or a salt thereof. The intermediate may be in the form of a salt of the intermediate. Such salts need not be a pharmaceutically-acceptable salt. For example it may be useful to prepare an intermediate in the form of a pharmaceutically non-acceptable salt if, for example, such salts are useful in the manufacture of a compound of formula (I).

In one aspect, particular intermediate compounds of the invention include, for example, one or more intermediate compounds of the formula (III) selected from:

2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidine;

2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidine;

2-[3-(thiazol-2-yl)isoxazol-5-yl]pyrrolidine;

2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidine;

2-[3-(2-cyanopyrid-3-yl)isoxazol-5-yl]pyrrolidine; and

2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidine;

and salts thereof.

In another aspect, particular intermediate compounds of the invention include, for example, one or more intermediate compounds of the formula (III-Pg^1) selected from:

N-tert-butyloxycarbonyl-2-(3-(2-pyridyl)isoxazol-5-yl)pyrrolidine;

N-tert-butyloxycarbonyl-2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidine;

N-tert-butyloxycarbonyl-2-(3-(thiazol-2-yl)isoxazol-5-yl)pyrrolidine;

N-(tert-butoxycarbonyl)-2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidine;

N-(tert-butoxycarbonyl)-2-[3-(2-cyanopyrid-3-yl)isoxazol-5-yl]pyrrolidine;

N-tert-butyloxycarbonyl-2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidine;

and salts thereof.

In another aspect, particular intermediate compounds of the invention include, for example, one or more intermediate compounds of the formula (III) selected from:

S-2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidine;

S-2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidine;

S-2-[3-(thiazol-2-yl)isoxazol-5-yl]pyrrolidine;

S-2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidine;

S-2-[3-(2-cyanopyrid-3-yl)isoxazol-5-yl]pyrrolidine; and

S-2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidine;

and salts thereof.

In another aspect, particular intermediate compounds of the invention include, for example, one or more intermediate compounds of the formula (III-Pg^1) selected from:

S-*N*-tert-butyloxycarbonyl-2-(3-(2-pyridyl)isoxazol-5-yl)pyrrolidine;

S-*N*-tert-butyloxycarbonyl-2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidine;

S-*N*-tert-butyloxycarbonyl-2-(3-(thiazol-2-yl)isoxazol-5-yl)pyrrolidine;

S-*N*-(tert-butoxycarbonyl)-2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidine;

S-N-(tert-butoxycarbonyl)-2-[3-(2-cyanopyrid-3-yl)isoxazol-5-yl]pyrrolidine;

S-*N*-tert-butyloxycarbonyl-2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidine;

and salts thereof.

The activity and selectivity of compounds according to the invention may be determined using an appropriate assay as described, for example, in WO 03/048133, and detailed below.

Biological Assays

IGF-1R Kinase Assay

a) Protein cloning, expression and purification

A DNA molecule encoding a fusion protein containing glutathione-S-transferase (GST), thrombin cleavage site and IGF-1R intracellular domain (amino-acids 930-1367) and subsequently referred to as GST-IGFR, was constructed and cloned into pFastBac1 (Life Technologies Ltd, UK) using standard molecular biology techniques (Molecular Cloning - A

Laboratory Manual, Second Edition 1989; Sambrook, Fritsch and Maniatis; Cold Spring Harbour Laboratory Press).

Production of recombinant virus was performed following the manufacturer's protocol. Briefly, the pFastBac-1 vector containing GST-IGFR was transformed into *E. coli* DH10Bac cells containing the baculovirus genome (bacmid DNA) and via a transposition event in the cells, a region of the pFastBac vector containing gentamycin resistance gene and the GST-IGFR expression cassette including the baculovirus polyhedrin promoter was transposed directly into the bacmid DNA. By selection on gentamycin, kanamycin, tetracycline and X-gal, resultant white colonies should contain recombinant bacmid DNA encoding GST-IGFR. Bacmid DNA was extracted from a small scale culture of several BH10Bac white colonies and transfected into Spodoptera frugiperda Sf21 cells grown in TC100 medium (Life Technologies Ltd, UK) containing 10% serum using CellFECTIN reagent (Life Technologies Ltd, UK) following the manufacturer's instructions. Virus particles were harvested by collecting cell culture medium 72 hrs post transfection. 0.5 ml of medium was used to infect 100 ml suspension culture of Sf21s containing 1 x 10^7 cells/ml. Cell culture medium was harvested 48 hrs post infection and virus titre determined using a standard plaque assay procedure. Virus stocks were used to infect Sf9 and "High 5" cells at a multiplicity of infection (MOI) of 3 to ascertain expression of recombinant GST-IGFR .

The GST-IGFR protein was purified by affinity chromatography on Glutathione-Sepharose followed by elution with glutathione. Briefly, cells were lysed in 50mM HEPES pH 7.5 (Sigma, H3375), 200mM NaCl (Sigma, S7653), Complete Protease Inhibitor cocktail (Roche, 1 873 580) and 1mM DTT (Sigma, D9779), hereinafter referred to as lysis buffer. Clarified lysate supernatant was loaded through a chromatography column packed with Glutathione Sepharose (Amersham Pharmacia Biotech UK Ltd.). Contaminants were washed from the matrix with lysis buffer until the UV absorbance at 280nm returned to the baseline. Elution was carried out with lysis buffer containing 20mM reduced glutathione (Sigma, D2804) and fractions containing the GST fusion protein were pooled and dialysed into a glycerol-containing buffer comprising 50 mM HEPES, pH 7.5, 200 mM NaCl, 10% glycerol (v/v), 3 mM reduced glutathione and 1 mM DTT.

b) Kinase activity assay

The activity of the purified enzyme was measured by phosphorylation of a synthetic poly GluAlaTyr (EAY) 6:3:1 peptide (Sigma-Aldrich Company Ltd, UK, P3899) using an ELISA detection system in a 96-well format.

b.i) Reagents used

Stock solutions

200mM	HEPES, pH 7.4	stored at 4°C	(Sigma, H3375)
1M	DTT	stored at -20°C	(Sigma, D9779)
100mM	Na_3VO_4	stored at 4°C	(Sigma, S6508)
1M	$MnCl_2$	stored at 4°C	(Sigma, M3634)
1mM	ATP	stored at -20°C	(Sigma, A3377)
Neat	Triton X-100	stored at room temperature	(Sigma, T9284)
10mg/ml	BSA	stored at 4°C	(Sigma, A7888)

Enzyme solution

GST-IGF-1R fusion protein at 75ng/ml in 100mM HEPES, pH 7.4, 5mM DTT, 0.25mM Na_3VO_4, 0.25% Triton X-100, 0.25mg/ml BSA, freshly prepared.

Co-factor solution

100mM HEPES, pH 7.4, 60mM $MnCl_2$, 5mM ATP.

Poly EAY substrate

Sigma substrate poly (Glu, Ala, Tyr) 6:3:1 (P3899). Made up to 1 mg/ml in PBS and stored at -20°C.

Assay plates

Nunc Maxisorp 96 well immunoplates (Life Technologies Ltd, UK).

Antibodies

Anti-phosphotyrosine antibody, monoclonal from Upstate Biotechnology Inc., NY, USA (UBI 05-321). Dilute 3μl in 11ml PBS/T + 0.5% BSA per assay plate.

Sheep- anti-mouse IgG HRP-conjugated secondary antibody from Amersham Pharmacia Biotech UK Ltd. (NXA931). Dilute 20μl of stock into 11ml PBS/T + 0.5% BSA per assay plate.

TMB solution

Dissolve 1mg TMB tablet (Sigma T5525) into 1ml DMSO (Sigma, D8779) in the dark for 1 hour at room temperature. Add this solution to 9ml of freshly prepared 50mM phosphate-citrate buffer pH 5.0 + 0.03% sodium perborate [1 buffer capsule (Sigma P4922) per 100ml distilled water].

Stop solution is 1M H_2SO_4 (Fisher Scientific UK. Cat. No. S/9200/PB08).

Test compound

Dissolve in DMSO to 10mM then dilutions in distilled water to give a range from 200 to 0.0026μM in 1-2% DMSO final concentration in assay well.

b.ii) Assay protocol

The poly EAY substrate was diluted to 1μg/ml in PBS and then dispensed in an amount of 100μl per well into a 96-well plate. The plate was sealed and incubated overnight at 4°C. Excess poly EAY solution was discarded and the plate was washed (2x PBS/T; 250μl PBS per well), blotting dry between washes. The plate was then washed again (1x 50mM HEPES, pH 7.4; 250μl per well) and blotted dry (this is important in order to remove background phosphate levels). 10μl test compound solution was added with 40μl of kinase solution to each well. Then 50μl of co-factor solution were added to each well and the plate was incubated for 60 minutes at room temperature.

The plate was emptied (i.e. the contents were discarded) and was washed twice with PBS/T (250μl per well), blotting dry between each wash. 100μl of diluted anti-phosphotyrosine antibody were added per well and the plate was incubated for 60 minutes at room temperature.

The plate was again emptied and washed twice with PBS/T (250μl per well), blotting dry between each wash. 100μl of diluted sheep- anti-mouse IgG antibody were added per well and the plate was left for 60 minutes at room temperature. The contents were discarded and the plate washed twice with PBS/T (250μl per well), blotting dry between each wash. 100μl of TMB solution were added per well and the plate was incubated for 5-10 minutes at room temperature (solution turns blue in the presence horse radish peroxidase).

Reaction was stopped with 50μl of H_2SO_4 per well (turns the blue solution yellow) and the plate was read at 450nm in Versamax plate reader (Molecular Devices Corporation, CA, USA) or similar.

The compounds of the Examples were found to have an IC_{50} in the above test of less than 100μM.

c) Inhibition of IGF-stimulated cell proliferation

The construction of murine fibroblasts (NIH3T3) over-expressing human IGF-1 receptor has been described by Lammers *et al* (EMBO J, **8**, 1369-1375, 1989). These cells show a proliferative response to IGF-I which can be measured by BrdU incorporation into newly synthesised DNA. Compound potency was determined as causing inhibition of the IGF-stimulated proliferation in the following assay:

c.i) Reagents used:

Cell Proliferation ELISA, BrdU (colorimetric) [Boehringer Mannheim (Diagnostics and Biochemicals) Ltd, UK. Cat no. 1 647 229].

DMEM, FCS, Glutamine, HBSS (all from Life Technologies Ltd., UK).

Charcoal/Dextran Stripped FBS (HyClone SH30068.02, Perbio Science UK Ltd).

BSA (Sigma, A7888).

Human recombinant IGF-1 Animal/media grade (GroPep Limited ABN 78 008 176 298, Australia. Cat No. IU 100).

Preparation and Storage of IGF

100μg of lyophilised IGF was reconstituted in 100ul of 10mM HCl.

Add 400μl of 1mg/ml BSA in PBS

25μl aliquots @ 200μg/ml IGF-1

Stored at –20°C.

For Assay:

10μl of stock IGF + 12.5ml growth medium to give 8X stock of 160ng/ml.

Complete growth medium

DMEM, 10% FCS, 2mM glutamine.

Starvation medium

DMEM, 1% charcoal/dextran stripped FCS, 2mM glutamine.

Test Compound

Compounds are initially dissolved in DMSO to 10mM, followed by dilutions in DMEM + 1% FCS + glutamine to give a range from 100 to 0.0.45μM in 1- 0.00045% DMSO final concentration in assay well.

c.ii) Assay protocol

Day 1

Exponentially growing NIH3T3/IGFR cells were harvested and seeded in complete growth medium into a flat-bottomed 96 well tissue culture grade plate (Costar 3525) at $1.2x10^4$ cells per well in a volume of 100µl.

Day 2

Growth medium was carefully removed from each well using a multi-channel pipette. Wells were carefully rinsed three times with 200µl with HBSS. 100µl of starvation medium was added to each well and the plate was re-incubated for 24 hours.

Day 3

50µl of a 4X concentrate of test compound was added to appropriate wells. Cells were incubated for 30 minutes with compound alone before the addition of IGF. For cells treated with IGF, an appropriate volume (i.e. 25µl) of starvation medium was added to make a final volume per well up to 200µl followed by 25µl of IGF-1 at 160ng/ml (to give a final concentration of 20ng/ml). Control cells unstimulated with IGF also had an appropriate volume (i.e. 50µl) of starvation medium added to make final volume per well up to 200µl. The plate was re-incubated for 20 hours.

Day 4

The incorporation of BrdU in the cells (after a 4h incorporation period) was assessed using the BrdU Cell Proliferation Elisa according to the manufacturer's protocol.

The compounds of the Examples were found to have an IC_{50} in the above test of less than 50µM.

d) Mechanism of Action Assay

Inhibition of IGF-IR mediated signal transduction was determined by measuring changes in phosphorylation of IGF-IR, Akt and MAPK (ERK1 and 2) in response to IGF-I stimulation of MCF-7 cells (ATCC No. HTB-22). A measure of selectivity was provided by the effect on MAPK phosphorylation in response to EGF in the same cell line.

d.i) Reagents used:

RPMI 1640 medium, RPMI 1640 medium without Phenol Red, FCS, Glutamine (all from Life Technologies Ltd., UK).

Charcoal/Dextran Stripped FBS (HyClone SH30068.02, Perbio Science UK Ltd).

SDS (Sigma, L4390).

2-mercaptoethanol (Sigma, M6250).

Bromophenol blue (Sigma, B5525).

Ponceau S (Sigma, P3504).

Tris base (TRIZMA™ base, Sigma, T1503).

Glycine (Sigma, G7403).

Methanol (Fisher Scientific UK. Cat. No. M/3950/21).

Dried milk powder (Marvel™, Premier Brands UK Ltd.).

Human recombinant IGF-1 Animal/media grade (GroPep Limited ABN 78 008 176 298, Australia. Cat No. IU 100).

Human recombinant EGF (Promega Corporation, WI, USA. Cat. No. G5021).

Complete growth medium

RPMI 1640, 10% FCS, 2mM glutamine

Starvation medium

RPMI1640 medium without Phenol Red, 1% charcoal/dextran stripped FCS, 2mM glutamine.

Test Compound

Compounds were initially dissolved in DMSO to 10mM, followed by dilutions in RPMI 1640 medium without Phenol Red + 1% FCS + 2mM glutamine to give a range from 100 to 0.0.45μM in 1- 0.00045% DMSO final concentration in assay well.

Western transfer buffer

50mM Tris base, 40mM glycine, 0.04% SDS, 20% methanol.

Laemmli buffer x2:

100mM Tris-HCl pH6.8, 20% glycerol, 4% SDS.

Sample buffer x4:

200mM 2-mercaptoethanol, 0.2% bromophenol blue in distilled water.

Primary Antibodies

Rabbit anti-human IGF-1Rβ (Santa Cruz Biotechnology Inc., USA, Cat. No *sc*-713) Rabbit anti-insulin/IGF-1R [$pYpY^{1162/1163}$] Dual Phosphospecific (BioSource International Inc, CA, USA. Cat No. 44-8041).

Mouse anti-PKBα/Akt (Transduction Laboratories, KY, USA. Cat. No. P67220) Rabbit anti-Phospho-Akt (Ser473) (Cell Signalling Technology Inc, MA, USA. Cat. No.#9271).

Rabbit anti-p44/p42 MAP kinase (Cell Signalling Technology Inc, MA, USA. Cat. No.#9102).

Rabbit anti-Phospho p44/p42 MAP kinase (Cell Signalling Technology Inc, MA, USA. Cat. No.#9101).

Mouse anti-actin clone AC-40 (Sigma-Aldrich Company Ltd, UK, A4700).

Antibody dilutions

Antibody	**Dilution in PBST**	**Secondary antibody in PBST**
IGFR	1:200 with 5% milk	Anti-rabbit with 5% milk
Phospho-IGFR	1:1000 with 5% milk	Anti-rabbit with 5% milk
Akt	1:1000 with 5% milk	Anti-mouse with 5% milk

Antibody	Dilution in PBST	Secondary antibody in PBST
PhosphoAkt	1:1000 with 5% milk	Anti-rabbit with 5% milk
MAPK	1:1000 with 5% milk	Anti-rabbit with 5% milk
Phospho-MAPK	1:1000 with 5% milk	Anti-rabbit with 5% milk
Actin	1:1000 with 5% milk	Anti-mouse with 5% milk

Secondary antibodies

Goat anti-rabbit, HRP linked (Cell Signalling Technology Inc, MA, USA. Cat. No.#7074).

Sheep- anti-mouse IgG HRP-conjugated (Amersham Pharmacia Biotech UK Ltd. Cat. No. NXA931).

Dilute anti-rabbit to 1:2000 in PBST + 5% milk.

Dilute anti-mouse to 1:5000 in PBST + 5% milk.

d.ii) Assay Protocol

Cell treatment

MCF-7 cells were plated out in a 24 well plate at $1x10^5$ cells/well in 1ml complete growth medium. The plate was incubated for 24 hours to allow the cells to settle. The medium was removed and the plate was washed gently 3 times with PBS 2ml/well. 1ml of starvation medium was added to each well and the plate was incubated for 24 hours to serum starve the cells.

Then 25μl of each compound dilution was added and the cells and compound were incubated for 30 minutes at 37°C. After 30 minutes incubation of the compound, 25μl of IGF (for 20ng/ml final concentration) or EGF (for 0.1ng/ml final concentration) was added to each well as appropriate and the cells incubated with the IGF or EGF for 5 minutes at 37°C. The medium was removed (by pipetting) and then 100μl of 2x Laemmli buffer was added. The plates were stored at 4°C until the cells were harvested. (Harvesting should occur within 2 hours following addition of Laemmli buffer to the cells.)

To harvest the cells, a pipette was used to repeatedly draw up and expel the Laemmli buffer/cell mix and transfer into a 1.5ml Eppendorf tube. The harvested cell lysates were kept at -20°C until required. The protein concentration of each lysate could be determined using the DC protein assay kit (Bio-Rad Laboratories, USA, according to manufacturer's instructions).

Western blot technique

Cell samples were made up with 4x sample buffer, syringed with a 21 gauge needle and boiled for 5 minutes. Samples were loaded at equal volumes and a molecular weight ladder on 4-12% Bis-Tris gels (Invitrogen BV, The Netherlands) and the gels were run in an Xcell *SureLock*™ Mini-Cell apparatus (Invitrogen) with the solutions provided and according to the manufacturer's instructions. The gels were blotted onto Hybond C Extra™ membrane (Amersham Pharmacia Biotech UK Ltd.) for 1 hour at 30 volts in the Xcell *SureLock*™ Mini-Cell apparatus, using Western transfer buffer. The blotted membranes were stained with 0.1% Ponceau S to visualise transferred proteins and then cut into strips horizontally for multiple antibody incubations according to the molecular weight standards. Separate strips were used for detection of IGF-1R, Akt, MAPK and actin control.

The membranes were blocked for 1 hour at room temperature in PBST + 5% milk solution. The membranes were then placed into 3ml primary antibody solution in 4 well plates and the plates were incubated overnight at 4°C. The membranes were washed in 5ml PBST, 3 times for 5 minutes each wash. The HRP-conjugated secondary antibody solution was prepared and 5ml was added per membrane. The membranes were incubated for 1 hour at room temperature with agitation. The membranes were washed in 5ml PBST, 3 times for 5 minutes each wash. The ECL solution (SuperSignal ECL, Pierce, Perbio Science UK Ltd) was prepared and incubated with the membranes for 1 minute (according to manufacturer's instructions), followed by exposure to light sensitive film and development.

The compounds of the Examples were found to have an IC_{50} in the above test of less than 20μM.

By way of example, the following Table illustrates the activity of representative compounds according to the invention. Column 2 of the Table shows IC_{50} data from Test (c) described above for the inhibition of IGF-stimulated proliferation in murine fibroblasts (NIH3T3) over-expressing human IGF-1 receptor:

Example Number	IC_{50} (μM) – Test (c)
1	0.31
13	0.13

We have found that the compounds of the present invention possess anti-proliferative properties such as anti-cancer properties that are believed to arise from their IGF-1R tyrosine

kinase inhibitory activity. Furthermore, certain of the compounds according to the present invention possess substantially better potency against the IGF-1R tyrosine kinase than against other tyrosine kinases enzymes. Such compounds possess sufficient potency against the IGF-1R tyrosine kinase that they may be used in an amount sufficient to inhibit IGF-1R tyrosine kinase whilst demonstrating little, or significantly lower, activity against other tyrosine kinases. Such compounds are likely to be useful for the effective treatment of, for example, IGF-1R driven tumours.

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 IGF-1R tyrosine kinase, i.e. the compounds may be used to produce an IGF-1R tyrosine kinase modulatory or inhibitory effect in a warm-blooded animal in need of such treatment. Thus the compounds of the present invention provide a method for the treatment of malignant cells characterised by modulation or inhibition of the IGF-1R tyrosine kinase. Particularly the compounds of the invention may be used to produce an anti-proliferative and/or pro-apoptotic and/or anti-invasive effect mediated alone or in part by the modulation or inhibition of IGF-1R tyrosine kinase. Particularly, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours that are sensitive to modulation or inhibition of IGF-1R tyrosine kinase that is involved in the signal transduction steps which drive proliferation and survival of these tumour cells. Accordingly the compounds of the present invention are expected to be useful in the treatment and/or prevention of a number 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 tumours of lymphoid lineage, including acute lymphocytic leukaemia, B-cell lymphoma and Burketts lymphoma;

(3) hematopoietic tumours of myeloid lineage, including acute and chronic myelogenous leukaemias, promyelocytic leukaemia and multiple myeloma;

(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 expected to be especially useful in the treatment of tumours of the breast, colon and prostate and in the treatment of multiple myeloma.

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

Thus according to this aspect of the invention there is provided the use of a compound of 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-proliferative effect in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-proliferative effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt thereof, as hereinbefore defined.

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

According to a further aspect of the invention there is provided the use of a compound of 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-proliferative effect which effect is produced alone or in part by inhibiting IGF-1R tyrosine kinase in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-proliferative effect which effect is produced alone or in part by inhibiting IGF-1R tyrosine kinase 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 hereinbefore defined.

According to a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically-acceptable salt thereof, for use in the production of an anti-proliferative effect which effect is produced alone or in part by inhibiting IGF-1R tyrosine kinase in a warm-blooded animal such as man.

According to a further aspect of the present invention there is provided the use of a compound of formula (I), or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of a disease or medical condition (for example a cancer as mentioned herein) mediated alone or in part by IGF-1R tyrosine kinase.

According to a further feature of this aspect of the invention there is provided a method for treating a disease or medical condition (for example a cancer as mentioned herein) mediated alone or in part by IGF-1R tyrosine kinase 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 hereinbefore.

According to a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically-acceptable salt thereof, for use in the treatment of a disease or medical condition (for example a cancer as mentioned herein) mediated alone or in part by IGF-1R tyrosine kinase.

According to a further aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of those tumours which are sensitive to inhibition of IGF-1R tyrosine kinase involved in the signal transduction steps which lead to the proliferation of tumour cells.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of those tumours which are sensitive to inhibition of IGF-1R tyrosine kinase, involved in the signal transduction steps which lead to the proliferation and/or survival of tumour cells 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 hereinbefore.

According to a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically-acceptable salt thereof, for use in the prevention or treatment of those tumours which are sensitive to inhibition of IGF-1R tyrosine kinase, involved in the signal transduction steps which lead to the proliferation and/or survival of tumour cells.

According to a further aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in providing an IGF-1R tyrosine kinase inhibitory effect.

According to a further feature of this aspect of the invention there is provided a method for providing an IGF-1R tyrosine kinase 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 hereinbefore.

According to a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically-acceptable salt thereof, for use in providing an IGF-1R tyrosine kinase inhibitory effect.

According to a further aspect of the present invention there is provided the use of a compound of formula (I), or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of a cancer, for example a cancer selected from leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS, breast, colorectal, cervical, endometrial, gastric, head and neck, hepatic, lung, muscle, neuronal, oesophageal, ovarian, pancreatic, pleural/peritoneal membranes, prostate, renal, skin, testicular, thyroid, uterine and vulval cancer.

According to a further feature of this aspect of the invention there is provided a method for treating a cancer, for example a cancer selected from selected from leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS, breast, colorectal, cervical, endometrial, gastric, head and neck, hepatic, lung, muscle, neuronal, oesophageal, ovarian, pancreatic, pleural/peritoneal membranes, prostate, renal, skin, testicular, thyroid, uterine and vulval cancer 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 hereinbefore.

According to a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically-acceptable salt thereof, for use in the treatment of a cancer, for example a cancer selected from leukaemia, multiple myeloma, lymphoma, bile duct, bone, bladder, brain/CNS, breast, colorectal, cervical, endometrial, gastric, head and neck, hepatic, lung, muscle, neuronal, oesophageal, ovarian, pancreatic, pleural/peritoneal membranes, prostate, renal, skin, testicular, thyroid, uterine and vulval cancer.

As mentioned above the size of the dose required for the therapeutic or prophlyactic treatment of a particular disease will necessarily be varied depending upon, amongst other things, the host treated, the route of administration and the severity of the illness being treated.

The compounds of the invention may be administered in the form of a pro-drug, by which we mean a compound that is broken down in a warm-blooded animal, such as man, to

release a compound of the invention. A pro-drug may be used to alter the physical properties and/or the pharmacokinetic properties of a compound of the invention. A pro-drug can be formed when the compound of the invention contains a suitable group or substituent to which a property-modifying group can be attached. Examples of pro-drugs include *in vivo* cleavable ester derivatives that may be formed at a carboxylic acid or a hydroxy group in a compound of formula (I).

Accordingly, the present invention includes those compounds of formula (I) as defined hereinbefore when made available by organic synthesis and when made available within the human or animal body by way of cleavage of a pro-drug thereof. Accordingly, the present invention includes those compounds of formula (I) that are produced by organic synthetic means and also such compounds that are produced in the human or animal body by way of metabolism of a precursor compound, that is a compound of formula (I) may be a synthetically-produced compound or a metabolically-produced compound.

A suitable pharmaceutically-acceptable pro-drug of a compound of formula (I) is one that is based on reasonable medical judgement as being suitable for administration to the human or animal body without undesirable pharmacological activities and without undue toxicity.

Various forms of pro-drug have been described, for example in the following documents :

a) Methods in Enzymology, Vol. 42, p. 309 to 396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) Design of Pro-drugs, edited by H. Bundgaard, (Elsevier, 1985);

c) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Pro-drugs", edited by H. Bundgaard, p. 113 to 191 (1991);

d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1 to 38 (1992); and

e) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988).

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 (active ingredient) is in association with a pharmaceutically-acceptable adjuvant, diluent or carrier.

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

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

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 amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of formula (I) 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 using a compound of formula (I) for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.1 mg/kg to 75 mg/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, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of this invention.

The anti-proliferative treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compounds 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 iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) 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™] and the anti-erbB1 antibody cetuximab [Erbitux, C225]); 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, ZD1839), *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 AZD1152, 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 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474; Example 2 within WO 01/32651), 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), vatalanib (PTK787; WO 98/35985) and SU11248 (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 $\alpha v\beta 3$ function and angiostatin)];

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

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

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

According to this aspect of the invention there is provided a pharmaceutical product comprising a compound of formula (I), or a pharmaceutically-acceptable salt thereof, as defined hereinbefore and an additional anti-tumour agent as defined hereinbefore for the conjoint treatment of cancer.

Although the compounds of formula (I) are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of IGF-1R tyrosine kinases. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

Examples

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

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

(ii) organic solutions were dried over anhydrous magnesium sulfate; 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) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;

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

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

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

(vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz, in DMSO-d_6 unless otherwise indicated. The following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Where NMR spectra are broad (due to hindered rotation or slow proton exchange), NMR spectra were run at 100°C;

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

(ix) solvent ratios are given in volume:volume (v/v) terms; and

(x) mass spectra were run with an electron energy of 70 electron volts in the chemical ionization (CI) mode using a direct exposure probe; where indicated ionization was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported; and unless otherwise stated, the mass ion quoted is $(MH)^+$;

(xi) the following abbreviations have been used:

THF	tetrahydrofuran;
EtOAc	ethyl acetate;
DCM	dichloromethane;
DMSO	dimethylsulfoxide;
DIPEA	N,N-diisopropylethylamine;
NMP	N-methylpyrrolid-2-one;
tBuOH	tert-butyl alcohol;

TFA	trifluoroacetic acid;
DMF	N,N-dimethylformamide; and
DMA	N,N-dimethylacetamide.

Example 1

S-6-Methyl-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine

A mixture of 2-chloro-6-methyl-4-(pyrid-2-ylamino)pyrimidine (229mg, 1.03mmol), S-2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidine (267 mg, 1.24mmol) and N,N-diisopropylethylamine (186mg, 1.44mmol) in n-hexanol (5.0ml) was heated at 150°C for 1 hour under microwave irradiation. The reaction mixture was poured on to a 50g isolute SCX-2 ion exchange column. The column was eluted with methanol to elute any neutrals, followed by 7M methanolic ammonia to elute the product. The solvent was removed by evaporation and the residue purified by chromatography on silica gel eluting with DCM and then with methanol / DCM (2:98) to give the title compound (100 mg, 24.3%) as a gum; NMR Spectrum (DMSO-d_6 + d_4-acetic acid at 100°C) 2.10 (m, 3H), 2.37 (m, 1H), 3.70 (m, 1H), 3.80 (m, 1H), 5.45 (d, 1H), 6.49 (s, 1H), 6.66 (s, 1H), 6.86 (m, 1H), 7.41 (m, 1H), 7.59 (t, 1H), 7.85 (m, 1H), 7.92 (d, 1H), 8.18 (d, 1H), 8.61 (d, 1H); Mass Spectrum 400 [MH]+.

The 2-chloro-6-methyl-4-(pyrid-2-ylamino)pyrimidine starting material was prepared as follows:

Sodium bis(trimethylsilyl)amide (1.6ml of a 2N solution in THF, 3.2mmol) was added to a solution of 6-methyl-2,4-dichloropyrimidine (348 mg, 2.13mmol) in THF (50ml) at ambient temperature. A solution of 2-aminopyridine (211mg, 2.24mmol) in THF (50ml) was added slowly to the reaction mixture. The reaction mixture was then stirred at ambient temperature for 18 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and the THF removed by evaporation. The aqueous residue was then extracted with DCM and the solvent removed from the organic layer by evaporation. The residue was purified by chromatography on silica gel eluting with methanol / DCM (0:100 increasing in polarity to 5:95). The purified product was recrystallised from diethylether/isohexane to give 2-chloro-6-methyl-4-(pyrid-2-ylamino)pyrimidine (242mg, 51%) as a solid; NMR Spectrum 2.35 (s, 3H), 7.03 (m, 1H), 7.50 (d, 1H), 7.71 (s, 1H), 7.75 (t, 1H), 8.32 (d, 1H), 10.5 (s, 1H); Mass Spectrum 221 [MH]+.

The *S*-2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidine was prepared as follows:

A 13% solution of sodium hypochlorite in water (4.6ml) was added over 2 hours to a vigorously stirred solution of S-*N*-tert-butoxycarbonyl-2-ethynylpyrrolidine (prepared as described in Bull. Soc. Chim. Fr. 1997, 134, 141-144 and J. Med. Chem. 1994, 37, 4455-4463) (1.0g, 5.2mmol) and pyrid-2-ylcarboxaldehyde oxime (577mg, 4.72mmol) in DCM (15ml) at -3°C. After the addition was complete, the reaction was stirred at 0°C for 2.5 hours. The mixture was then diluted with water and DCM and the layers partitioned and separated. The organic layer was washed in turn with water and brine, dried (Na_2SO_4) and the volatiles removed by evaporation. The residue was purified by chromatography on silica gel eluting with 10% isohexane / ethyl acetate (90:10 increasing in polarity to 75:25) to give S-*N*-tert-butyloxycarbonyl-2-(3-(2-pyridyl)isoxazol-5-yl)pyrrolidine (0.69g, 47%) as a waxy solid; NMR Spectrum (Major rotamer): 1.4 (s, 9H), 1.95 (m, 3H), 2.28 (m, 1H), 3.35 (m, 1H), 3.5 (m, 1H), 5.0 (s, 1H), 6.76 (s, 1H), 7.5 (m, 1H), 7.97 (m, 2H), 8.68 (d, 1H); Mass Spectrum 316 [MH]+; Rotation α_D = - 104.8 (c=1.0, methanol).

TFA (2.3ml) was added over 10 minutes to a stirred solution of S-*N*-tert-butyloxycarbonyl-2-(3-(2-pyridyl)isoxazol-5-yl)pyrrolidine (0.744g, 2.36mmol) in DCM (12ml) at 0°C. The reaction was stirred at 0°C for 1 hour and then at ambient temperature for 18 hours. The volatiles were removed by evaporation and the residue dissolved in distilled water (23ml). The solution was adjusted to pH 10.5 by careful addition of solid sodium carbonate and then 40% aqueous sodium hydroxide solution near the end point. The aqueous solution was the extracted with DCM (x4), the organic extracts were combined, dried (Na_2SO_4) and the solvent removed by evaporation to give S-2-(3-(2-pyridyl)isoxazol-5-yl)pyrrolidine (0.446g, 88%) as a gum; NMR Spectrum 1.8 (m, 3H), 2.13 (m, 1H), 2.9 (t, 2H), 4.35 (t, 1H), 6.8 (s, 1H), 7.48 (t, 1H); 7.96 (m, 2H), 8.67 (d, 1H); Mass Spectrum 216 [MH]+; Rotation α_D = –15.2 (c=1.0, methanol).

Example 2

S-6-Chloro-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine

A mixture of 2,6-dichloro-4-(pyrid-2-ylamino)pyrimidine (401mg, 1.66mmol), S-2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidine (395mg, 1.83mmol) and N,N-diisopropylethylamine (259mg, 1.99mmol) in n-butanol (30ml) was heated at 70°C for 18 hours. The volatiles were removed by evaporation and the residue purified by chromatography on silica gel eluting with EtOAc/isohexane (10:90 increasing in polarity to 40:60) and then with methanol/DCM

(10:90) to give the title compound (360mg, 52%) as a foam; NMR Spectrum (DMSO-d_6 + d_4-acetic acid at 100°C) 2.11 (m, 3H), 2.40 (m, 1H), 3.68 (m, 1H), 3.77 (m, 1H), 5.42 (m, 1H), 6.71 (d, 1H), 6.92 (m, 1H), 7.40 (m, 1H), 7.61 (t, 1H), 7.75 (d, 1H), 7.85 (t, 1H), 7.92 (d, 1H), 8.21 (d, 1H), 8.62 (d, 1H); Mass Spectrum 420 [MH]+.

The 2,6-dichloro-4-(pyrid-2-ylamino)pyrimidine starting material was prepared as follows:

Sodium bis(trimethylsilyl)amide (19.3ml of 2N solution in THF, 38.4mmol) was added slowly to a solution of 2,4,6-trichloropyrimidine (5.88g, 32.0mmol) and 2-aminopyridine (3.175g, 33.6mmol) in THF (200 ml) at 0°C. The reaction mixture was stirred at 0°C for 2 hours and then ambient temperature for 18 hours. The mixture was cooled 0°C and quenched at with water and the THF removed by evaporation. The resulting aqueous suspension was filtered and the solid isolated then triturated with diethylether. The filtrate obtained was evaporated to a gum and redissolved in DCM and purified by chromatography on silica gel eluting with DCM (100%) and 10-40% EtOAc/isohexane. The solid obtained after evaporation was triturated with isohexane to give 2,6-dichloro-4-(pyrid-2-ylamino)pyrimidine as a solid (1.12g, 14.5%); NMR Spectrum 7.10 (m, 1H), 7.42 (d, 1H), 7.80 (t, 1H), 8.07 (br s, 1H), 8.38 (d, 1H); Mass Spectrum 241 [MH]+.

Example 3

S-6-Morpholino-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine

A mixture of S-6-chloro-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine (333mg, 0.79mmol) and morpholine (20g) was heated at 130°C for 2 hours. The mixture was allowed to cool and the volatiles were removed by evaporation. The residue dissolved in DCM then purified by chromatography on silica gel eluting with methanol/DCM (0:100 increasing in polarity to 10:90) to give the title compound (280mg, 75%) as a foam; NMR Spectrum 2.09 (m, 3H), 2.39 (m, 1H), 3.40 (m, 4H), 3.60 (m, 4H), 3.70 (m, 1H), 3.78 (m, 1H), 5.39 (d, 1H), 6.08 (s, 1H), 6.67 (s, 1H), 6.82 (m, 1H), 7.43 (t, 1H), 7.55 (t, 1H), 7.84 (m, 1H), 7.91 (m, 2H), 8.15 (d, 1H), 8.64 (d, 1H), 8.77 (s, 1H); Mass Spectrum 471 [MH]+.

Example 4

S-6-Methoxy-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine

A mixture *S*-6-chloro-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-[*N*-(tert-butylcarbonyl)pyrid-2-ylamino]pyrimidine (480mg, 0.93mmol) and sodium methoxide (529mg, 9.80mmol) in methanol (5ml) was heated at 66°C for 1 hour under microwave irradiation. The reaction mixture was allowed to cool and quenched with saturated aqueous ammonium chloride solution. The volatiles were removed by evaporated and the aqueous residue extracted with DCM. The solvent was removed from the extracts by evaporation and the residue purified by chromatography on silica gel eluting with DCM (100%) and 2-5% methanol/DCM (0:100 increasing in polarity to 5:95). The purified product was recrystallised from diethylether/isohexane and collected by filtration to give the title compound (54mg, 14%) as a solid; NMR Spectrum 2.13 (m, 3H), 2.39 (m, 1H), 3.55 (m, 1H), 3.70 (m, 1H), 3.76 (s, 3 H), 5.47 (d, 1H), 6.55 (s, 1H), 6.75 (s, 1H), 6.86 (m, 1H), 7.45 (m, 1H), 7.61 (m, 2H), 7.90 (t, 1H), 7.95 (d, 1H), 8.21 (d, 1H), 8.66 (d, 1H), 9.16 (s, 1H); Mass Spectrum 416 [MH]+.

The S-6-chloro-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-[*N*-(tert-butylcarbonyl)pyrid-2-ylamino]pyrimidine starting material was prepared as follows:

Lithium bis(trimethylsilyl)amide (2.91ml of a 1N of a solution in THF, 2.90mmol) was added slowly to a solution of 2,6-dichloro-4-(pyrid-2-ylamino)pyrimidine (500mg, 2.07mmol), and di-tert-butyl dicarbonate (590mg, 2.69mmol) in THF (100ml) at 0°C. The reaction mixture was stirred at 0°C for 1 hour, then at ambient temperature for 3 hours and finally at heated at 50°C for 3 hours. The reaction was allowed to cool, quenched with water then extracted with diethylether. The solvent was removed from the organic layer by evaporation and the residue purified by chromatography on silica gel eluting with isohexane/DCM (100:0 increasing in polarity to 0:100) and then with diethylether to give 2,6-dichloro-4-[*N*-(tert-butylcarbonyl)pyrid-2-ylamino]pyrimidine (629mg, 89%) as a gum; NMR Spectrum 1.40 (s, 9H), 7.45 (m, 2H), 7.95 (t, 1H), 8.03 (s, 1H), 8.50 (d, 1H); Mass Spectrum 241 [MH]+.

A mixture of 2,6-dichloro-4-[*N*-(tert-butylcarbonyl)pyrid-2-ylamino]pyrimidine (629mg, 1.84mmol), S-2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidine (436mg, 2.02mmol) and N,N-diisopropylethylamine (286mg, 2.21mmol) in n-butanol (30ml) was heated at 70°C for 18 hours. The mixture was allowed to cool and the volatiles removed by evaporation. The

residue was purified by chromatography on silica gel eluting with methanol/DCM (0:100 increasing in polarity to 5:95) to give S-6-chloro-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-[*N*-(tert-butylcarbonyl)pyrid-2-ylamino]pyrimidine (480mg, 50%) as an oil; Mass Spectrum 420 [MH]+.

Example 5

S-6-Methyl-2-{2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine

A mixture of 2-chloro-6-methyl-4-(pyrid-2-ylamino)pyrimidine (100mg, 0.45mmol), S-2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidine (110mg, 0.45mmol), N,N-diisopropylethylamine (0.16ml, 0.90mmol) and n-hexanol (2ml) were heated at 130°C for 40 minutes. The reaction mixture was allowed to cool and then directly purified by reverse phase HPLC using a C18 column eluting with water / acetonitrile / TFA (95:5:0.2 decreasing in polarity to 0:100:0.2). Product containing fractions were combined and passed through a 50g isolute SCX-2 ion exchange column. The column was eluted with methanol to elute any neutrals, followed by 7M methanolic ammonia to elute the product. The solvent was removed by evaporation to give the title compound (35mg, 18 %) as a white foam; NMR Spectrum 2.10 (m, 3H), 2.14 (s, 3H), 2.39 (m, 1H), 3.76 (m, 2H), 3.98 (s, 3H), 5.49 (dd, 1H), 6.54 (s, 1H), 6.67 (s, 1H), 6.92 (m, 1H), 7.60 (t, 1H), 7.85 (d, 1H), 8.22 (dd, 1H), 8.29 (s, 2H), 9.14 (s, 1H); Mass Spectrum 431 [MH]+.

The S-2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidine starting material was prepared as follows:

A mixture of 3-methoxypyrazine-2-carboxaldehyde (Tetrahedron (1999), 56(2), 265-273) (2.1g, 15mmol), hydroxylamine hydrochloride (1.27g, 18mmol), ethanol (20ml) and triethylamine (4.17ml, 30mmol) was heated at 60°C for 90 minutes. The volatiles were removed by evaporation and residue was purified by column chromatography on silica gel eluting with hexane / EtOAc (100:0 increasing in polarity 0:100) to give 3-methoxypyrazine-2-carboxaldehyde oxime (740mg, 32%) as a white solid; NMR Spectrum 3.96 (s, 3H), 8.22 (s, 2H), 8.23 (m, 1H), 11.89 (s, 1H).

Sodium hypochlorite (5.23ml of a 13% aqueous solution, 9.16mmol) was slowly added to a stirred mixture of S-N-tert-butoxycarbonyl-2-ethynylpyrrolidine (prepared as described in Bull. Soc. Chim. Fr. 1997, 134, 141-144 and J. Med. Chem. 1994, 37, 4455-4463) (1.07g, 5.50mmol), 3-methoxypyrazine-2-carboxaldehyde oxime (Method 67) (0.7g,

4.58mmol) in DCM (40 ml) cooled to 0°C. The reaction was allowed to warm to ambient temperature and then stirred for 12 hours. The layers were separated, the solvent removed from the organic layer and the residue purified by column chromatography on silica gel eluting with hexane / EtOAc (100:0 increasing in polarity 0:100). The purified product solidified to a solid on standing and was dissolved in TFA (10ml) and the mixture stirred at ambient temperature for 30 minutes. The volatiles were removed by evaporation and the residue dissolved in DCM and poured onto an isolute SCX-2 ion exchange column. The column was eluted with methanol to elute any neutrals, followed by 7M methanolic ammonia to elute the product. The solvent was removed by evaporation to give S-2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidine (260mgs, 23 %) as a brown oil; NMR Spectrum 1.78 (m, 3H), 2.14 (m, 1H), 2.92 (t, 2H), 4.01 (s, 3H), 4.36 (dd, 1H), 6.78 (s, 1H), 8.36 (s, 2H); Mass Spectrum 247 [MH]+.

Example 6

S-6-Methyl-2-{2-[3-(thiazol-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine

A mixture of 2-chloro-6-methyl-4-(pyrid-2-ylamino)pyrimidine (100mg, 0.45mmol), S-2-[3-(thiazol-2-yl)isoxazol-5-yl]pyrrolidine (100mg, 0.45mmol), N,N-diisopropylethylamine (0.16ml, 0.90mmol) and n-hexanol (2ml) were heated at 130°C for 40 minutes. The reaction mixture was allowed to cool and then directly purified by reverse phase HPLC using a C18 column eluting with water / acetonitrile / TFA (95:5:0.2 decreasing in polarity to 0:100:0.2). Product containing fractions were combined and passed through a 50g isolute SCX-2 ion exchange column. The column was eluted with methanol to elute any neutrals, followed by 7M methanolic ammonia to elute the product (27mg, 15 %) as a white foam; NMR Spectrum 2.10 (m, 3H), 2.16 (s, 3H), 2.39 (m, 1H), 3.76 (m, 2H), 5.47 (dd, 1H), 6.50 (s, 1H), 6.67 (s, 1H), 6.90 (m, 1H), 7.59 (t, 1H), 7.81 (s 1H), 7.85 (d, 1H), 8.01 (d, 1H), 8.22 (d, 1H), 9.14 (s, 1H); Mass Spectrum 406.5 [MH]+.

The S-2-[3-(thiazol-2-yl)isoxazol-5-yl]pyrrolidine starting material was prepared as follows:

N-Chlorosuccinimide (10.6g, 80mmol) was added in portions to a solution of thiazole-2-carboxaldehyde oxime (10.35g, 80mmol) in DMF (30ml) cooled to -5°C. The reaction was stirred at -5°C for 1 hour, allowed to warm slowly to ambient temperature over 3 hours. The mixture was diluted with ether, EtOAc and water. The solid product was collected by

filtration. The organic layer was separated washed with water and brine, dried (Na_2SO_4) and the solvent removed by evaporation, keeping the bath temperature at ambient temperature, to give solid product. The two batches of solid were combined and directly dissolved in THF (200ml) and the solution added dropwise to a solution of S-N-tert-butoxycarbonyl-2-ethynylpyrrolidine (prepared as described in Bull. Soc. Chim. Fr. 1997, 134, 141-144 and J. Med. Chem. 1994, 37, 4455-4463) (31g, 160mmol) and triethylamine (13.4ml, 96mmol) in THF (200ml) cooled to 0°C, the mixture was allowed to slowly warm to ambient temperature and stirred for 18 hours. The solvent was removed by evaporation, water added to the residue and the mixture extracted with DCM. The extracts were combined, washed with brine, dried (Na_2SO_4) and the solvent removed by evaporation. The residue was purified by column chromatography on silica gel eluting with EtOAc / hexane (1:4 increasing in polarity to 1:1) to elute first recovered starting acetylene and then to give S-*N*-tert-butyloxycarbonyl-2-(3-(thiazol-2-yl)isoxazol-5-yl)pyrrolidine (8.32g, 32%) as an orange oil; NMR Spectrum 1.22 and 1.38 (2x br s, 9H), 1.85 (m, 3H), 2.15 (br m, 1H), 3.37 (m, 1H), 3.50 (m, 1H), 5.00 (br m, 1H), 6.78 and 6.83 (2x br s, 1H), 7.97 (d, 1H), 8.05 (d, 1H); Mass Spectrum 266 [MH-C_4H_9]+.

3M Hydrochloric acid (26ml) was added to a solution of *S-N*-tert-butyloxycarbonyl-2-(3-(thiazol-2-yl)isoxazol-5-yl)pyrrolidine (8.32g, 26mmol) in methanol (26ml) and the mixture stirred at ambient temperature for 18 hours and then at 60°C for 1 hour. The volatiles were removed by evaporation, the aqueous layer was washed with DCM, adjusted to pH 11-12 with 40% aqueous sodium hydroxide solution and extracted with DCM (x6). The extracts were combined, dried (Na_2SO_4) and the solvent removed by evaporation. The residue was purified by column chromatography on silica gel eluting with methanol / DCM (5:95) to give S-2-(3-(thiazol-2-yl)isoxazol-5-yl)pyrrolidine (4.01g, 70%) as a yellow oil; NMR Spectrum 1.75 (m, 3H), 2.10 (m, 1H), 2.89 (t, 2H), 4.33 (m, 1H), 6.78 (s, 1H), 7.95(d, 1H), 8.03 (d, 1H); Mass Spectrum 222 [MH]+.

Example 7

S-6-Ethyl-2-{2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine

A mixture of the 2-chloro-6-ethyl-4-(pyrid-2-ylamino)pyrimidine (184mg, 0.78mmol), S-2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidine (252mg, 1.09mmol) and N,N-diisopropylethylamine (0.41ml, 2.34mmol) in n-hexanol (10ml) was heated at 130°C,

under nitrogen for 18 hours. The mixture was allowed to cool and the hexanol removed by pouring mixture on to an SCX2 ion exchange column and eluting with methanol. The product was eluted with 7M methanolic ammonia. The volatiles were removed by evaporation and the residue purified by column chromatography on silica gel, eluting with EtOAc / isohexane (35:65) to give the title compound (24mg, 8%); NMR Spectrum 1.16 (t, 3H), 2.0-2.2 (m, 3H), 2.48-2.53 (m, 3H), 2.76 (s, 3H), 3.65-3.75 (m, 1H), 3.75-3.85 (m, 1H), 5.49 (d, 1H), 6.53 (s, 1H), 6.70 (s, 1H), 6.89 (dd, 1H), 7.60 (dd, 1H), 8.89 (d, 1H), 8.20 (d, 1H), 8.57 (s, 2H), 9.18 (s, 1H); Mass Spectrum 429 [MH]+.

The 2-chloro-6-ethyl-4-(pyrid-2-ylamino)pyrimidine starting material was prepared as follows:

A mixture of 2,4-dichloro-6-ethylpyrimidine (J. Am. Chem. Soc. 1936, 58, 78) (1.7g, 9.6mmol), 2-aminopyridine (701mg, 7.45mmol) and cesium carbonate (3.4g, 10.5mmol) in 1,4-dioxane (50ml) was purged with nitrogen for 10 minutes. 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (375mg, 0.64mmol), tris(dibenzylideneacetone) dipalladium(0) (375mg, 0.42mmol) were added and heated to 100°C for 1.5 hours. The mixture was allowed to cool, washed with water and dried (Na_2SO_4) and the solvent removed by evaporation. The residue was purified by column chromatography on silica gel eluting with EtOAc / isohexane (0:100 increasing in polarity to 15:85) to give 2-chloro-6-ethyl-4-(pyrid-2-ylamino)pyrimidine (290mg, 13%); NMR Spectrum 1.20 (t, 3H), 2.64 (q, 2H), 7.05 (dd, 1H), 7.55 (d, 1H), 7.71 (s, 1H), 7.78 (dd, 1H), 8.34 (d, 1H), 10.52(s, 1H); Mass Spectrum 235 [MH]+.

The S-2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidine starting material was prepared as follows:

A mixture of 2,3-dimethylpyrazine (20g, 18.5mmol), selenium dioxide (41.06g, 37mmol) and diatomeous earth (20g) in EtOAc (500ml) was stirred and heated at 70°C for 2 hours. The mixture was allowed to cool and the insoluble matter was removed by filtration through diatomeous earth. The filtrate was washed with saturated aqueous sodium hydrogen carbonate solution and then saturated aqueous sodium chloride solution, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was suspended in water (100ml) and hydroxylamine (45ml of a 50% aqueous solution) was added. The mixture was stirred at ambient temperature for 18 hours and the mixture then extracted with EtOAc. The extracts were combined, washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was triturated with isohexane to give 3-

methylpyrazine-2-carboxaldehyde oxime (9.65g, 38%); NMR Spectrum 2.67 (s, 3H), 8.23 (s, 1H), 8.45-8.49 (m, 2H), 11.87 (s, 1H).

Sodium hypochlorite (18ml of a 13% aqueous solution, 25.9mmol) was added dropwise to a stirred suspension of 3-methylpyrazine-2-carboxaldehyde oxime (2.74g, 20mmol) and S-*N*-tertbutoxycarbonyl-2-ethynylpyrrolidine (prepared as described in Bull. Soc. Chim. Fr. 1997, 134, 141-144 and J. Med. Chem. 1994, 37, 4455-4463) (5.85g, 30mmol) in DCM (50ml) at 0°C. The mixture was stirred for 1 hour at 0°C then allowed to warm to ambient temperature and stirred for 18 hours. The mixture was diluted with water and extracted with DCM. The extracts were combined, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by chromatography on silica gel eluting first with DCM and then with EtOAc/isohexane (25:75) to give S-*N*-(tert-butoxycarbonyl)-2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidine (2.62g, 48%); Mass Spectrum 275 [M-C_4H_9]+.

TFA (20ml) was added to a solution of S-*N*-(tert-butoxycarbonyl)-2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidine (2.6g, 7.9mmol) in DCM (100ml) and the mixture stirred for 18 hours at ambient temperature. The volatiles were removed by evaporation and the residue dissolved in water. The aqueous mixture was adjusted to pH10-11 with 40% aqueous sodium hydroxide solution and extracted with DCM. The extracts were combined, dried ($MgSO_4$) and the solvent removed by evaporation to give S-2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidine (1.69g, 93%) as an oil; NMR Spectrum ($CDCl_3$) 1.81-2.04 (m, 3H), 2.17 (s, 1H), 2.19-2.32 (m, 1H), 2.91 (s, 3H), 3.03-3.19 (m, 2H), 4.41-4.50 (m, 1H), 6.77 (s, 1H), 8.51 (s, 2H); Mass Spectrum 231 [MH]+.

Example 8

S-6-Methyl-2-{2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine

A mixture of the 2-chloro-6-methyl-4-(pyrid-2-ylamino)pyrimidine (172mg, 0.78mmol), S-2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidine (252mg, 1.09mmol) and N,N-diisopropylethylamine (0.41ml, 2.34mmol) in n-hexanol (10ml) was heated at 130°C, under nitrogen for 18 hours. The mixture was allowed to cool and the hexanol removed by pouring mixture on to an SCX2 ion exchange column and eluting with methanol. The product was eluted with 7M methanolic ammonia. The volatiles were removed by evaporation and the residue purified by column chromatography on silica gel, eluting with

EtOAc / isohexane (40:60) to give the title compound (105mg, 33%); NMR Spectrum 2.05-2.15 (m, 3H), 2.20 (s, 3H), 2.35-2.45 (m, 1H), 2.76 (s, 3H), 3.68-3.72 (m, 1H), 3.75-3.85 (m, 1H), 5.50 (d, 1H), 6.50 (s, 1H), 6.68(s, 1H), 6.89 (dd, 1H), 7.60 (t, 1H), 7.85 (d, 1H), 8.20 (d, 1H), 8.56-8.58 (d, 2H), 9.20 (s, 1H); Mass Spectrum 415[MH]+.

The 2-chloro-6-methyl-4-(pyrid-2-ylamino)pyrimidine starting material was prepared as follows:

A mixture of 2,4-dichloro-6-methylpyrimidine (4.0g, 24.7mmol), 2-aminopyridine (1.65g,17.5mmol) and cesium carbonate (8.76g, 26.9mmol) in 1,4-dioxane (100ml) was purged with nitrogen for 10 minutes. 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (953mg, 1.62mmol), tris(dibenzylideneacetone)dipalladium(0) (953mg, 1.07mmol) were added and heated to 100°C for 1.5 hours. The mixture was allowed to cool, washed with water and dried (Na_2SO_4) and the solvent removed by evaporation. The residue was purified by column chromatography on silica gel eluting with EtOAc / isohexane (0:100 increasing in polarity to 15:85) to give 2-chloro-6-methyl-4-(pyrid-2-ylamino)pyrimidine (340mg, 7%); Mass Spectrum 221 [MH]+.

Example 9

S-6-Methyl-2-{2-[3-(2-cyanopyrid-3-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine

A mixture of the 2-chloro-6-methyl-4-(pyrid-2-ylamino)pyrimidine (150mg, 0.78mmol), S-2-[3-(2-cyanopyrid-3-yl)isoxazol-5-yl]pyrrolidine (263mg, 1.09mmol) and N,N-diisopropylethylamine (0.41ml, 2.34mmol) in n-hexanol (10ml) was heated at 130°C, under nitrogen for 18 hours. The mixture was allowed to cool and the hexanol removed by pouring mixture on to an SCX2 ion exchange column and eluting with methanol. The product was eluted with 7M methanolic ammonia. The volatiles were removed by evaporation and the residue purified by column chromatography on silica gel, eluting with EtOAc / isohexane (40:60) to give the title compound (70mg, 24%); NMR Spectrum 2.05-2.12 (m, 3H), 2.20 (s, 3H), 2.40-2.45 (m, 1H), 3.70-3.83 (m, 2H), 5.50 (d, 1H), 6.55 (s, 1H), 6.84 (s, 1H), 6.87-6.91 (m, 1H), 7.60 (t, 1H), 7.81-7.84 (m, 2H), 8.20(d, 1H), 8.30 (d, 1H), 8.80 (d, 1H), 9.15(s, 1H); Mass Spectrum 425[MH]+.

The S-2-[3-(2-cyanopyrid-3-yl)isoxazol-5-yl]pyrrolidine starting material was prepared as follows:

A solution of hydroxylamine hydrochloride (533mg, 7.6mmol) in water (1.8ml) was added dropwise to sodium hydroxide (708mg, 17mmol) in water (2ml). The

resulting solution was then added to a solution of 2-chloropyrid-3-ylcarboxaldehyde (1g, 7mmol) in ethanol (7ml), water (7ml) and ice (15g). The mixture was stirred at ambient temperature for 18 hours. The mixture was neutralised to pH 7 with 6M hydrochloric acid. The solid product was collected by filtration, washed with water and dried to give 2-chloropyrid-3-ylcarboxaldehyde oxime (800mg, 73%); NMR Spectrum 7.45 (dd, 1H), 8.18 (dd, 1H), 8.32 (s, 1H), 8.42 (dd, 1H); Mass Spectrum 157 [MH]+.

Sodium hypochlorite (5.3ml of a 13% aqueous solution) was added dropwise to a vigorously stirred suspension of 2-chloropyrid-3-ylcarboxaldehyde oxime (800mg, 5.1mmol) and S-N-tert-butoxycarbonyl-2-ethynylpyrrolidine (prepared as described in Bull. Soc. Chim. Fr. 1997, 134, 141-144 and J. Med. Chem. 1994, 37, 4455-4463) (1.99g, 10.2mmol) in DCM (20ml) at about 0 to 5°C. The mixture was allowed to warm and stirred at ambient temperature for 18 hours. The volatiles were removed by evaporation and the residue purified by chromatography on silica gel eluting with EtOAc / hexane (20:80) to give S-N-(tert-butoxycarbonyl)-2-[3-(2-chloropyrid-3-yl)isoxazol-5-yl]pyrrolidine (955mg, 54%); NMR Spectrum 1.22-1.42 (m, 9H), 1.95-2.0 (m, 3H), 2.22-2.38 (m, 1H), 3.30-3.40 (m, 1H), 3.43-3.55 (m, 1H), 5.0 (s, 1H), 6.78 (s, 1H), 7.58 (s, 1H), 8.12 (d, 1H), 8.55 (dd, 1H); Mass Spectrum 350 [MH]+.

A mixture of S-N-(tert-butoxycarbonyl)-2-[3-(2-chloropyrid-3-yl)isoxazol-5-yl]pyrrolidine (1.28g, 3.67mmol), copper(I)cyanide (1.31g, 14.7mmol), tris(dibenzylideneacetone)dipalladium(0) (134mg, 0.15mmol), 1,1'-bis(diphenylphosphino) ferrocene (479mg, 0.59mmol) and tetraethylammonium cyanide (574mg, 3.68mmol) in 1,4-dioxane (20ml) was thoroughly degassed by repeated evacuation and refilling with nitrogen and then the mixture was heated at reflux under nitrogen for 2 days. The mixture was allowed to cool and was diluted with EtOAc / methanol and insoluble matter was removed by filtration. The filtrate was washed with water and the organic layer separated, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by chromatography on silica gel eluting with EtOAc / hexane (30:70) to give S-N-(tert-butoxycarbonyl)-2-[3-(2-cyanopyrid-3-yl)isoxazol-5-yl]pyrrolidine (578mg, 47%); NMR Spectrum 1.22-1.42 (m, 9H), 1.89-2.0 (m, 3H), 2.23-2.39 (m, 1H), 3.37-3.43 (m, 1H), 3.43-3.54 (m, 1H), 5.02-5.12 (m, 1H), 6.96 (s, 1H), 7.89 (dd, 1H), 8.38 (d, 1H), 8.86 (dd,1H).

TFA (1ml) was added to a solution of S-N-(tert-butoxycarbonyl)-2-[3-(2-cyanopyrid-3-yl)isoxazol-5-yl]pyrrolidine (570mg, 1.67mmol) in DCM (5ml) and the mixture stirred for 3 days at ambient temperature. The volatiles were removed by evaporation and the residue dissolved in water. The aqueous mixture was adjusted to pH10-11 with 40% aqueous sodium hydroxide solution and extracted with DCM. The extracts were combined, dried (Na_2SO_4) and the solvent removed by evaporation. The residue was purified by chromatography on silica gel eluting with methanol / DCM (1:39) to give S-2-[3-(2-cyanopyrid-3-yl)isoxazol-5-yl]pyrrolidine (250mg, 63%); Mass Spectrum 241 [MH]+.

Example 10

S-6-Ethyl-2-{2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine

A mixture of the 2-chloro-6-ethyl-4-(pyrid-2-ylamino)pyrimidine (125mg, 0.53mmol), S-2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidine (171mg, 0.79mmol) and N,N-diisopropylethylamine (0.28ml, 1.6mmol) in n-hexanol (10ml) was heated at 130°C, under nitrogen for 18 hours. The mixture was allowed to cool and the hexanol removed by pouring mixture on to an SCX2 ion exchange column and eluting with methanol. The product was eluted with 7M methanolic ammonia. The volatiles were removed by evaporation and the residue purified by column chromatography on silica gel, eluting with EtOAc / isohexane (45:45) to give the title compound (77mg, 35%); NMR Spectrum 1.16 (t, 3H), 2.05-2.20 (m, 3H), 2.35-2.46 (m, 4H), 3.76-3.89 (m, 2H), 5.47 (d, 1H), 6.54 (s, 1H), 6.73 (s, 1H), 6.91 (t, 1H), 7.54 (t, 1H), 7.63 (dd, 1H), 7.89 (d, 1H), 8.22 (d, 1H), 8.91 (d, 1H), 9.19 (s, 1H); Mass Spectrum 415 [MH]+.

The S-2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidine starting material was prepared as follows:

13% Aqueous sodium hypochlorite solution (4.25ml, 7.45mmol) was slowly added to a mixture of S-N-*tert*-butoxycarbonyl-2-ethynylpyrrolidine (prepared as described in Bull. Soc. Chim. Fr. 1997, 134, 141-144 and J. Med. Chem. 1994, 37, 4455-4463) (1.45g, 7.45mmol) and pyrimidine-2-carbaldehyde oxime (0.47g, 3.82mmol, Khimiya Geterotsiklicheskikh Soedinenii (1972), 10, 1422-4) in DCM (15 ml) cooled to 0°C. The reaction mixture was allowed to warm to ambient temperature and then stirred for 12 hours. The mixture diluted with ethyl acetate, the layers were separated the solvent was removed from the organic layer by evaporation. The residue was purified by column chromatography

on silica gel eluting with EtOAc / hexane (0:100 increasingly in polarity to 100:0). The product fractions were evaporated to give a golden oil which solidified to a solid on standing (250mg, 20 %). This solid was then dissolved in TFA (2ml) and stirred at ambient temperature for 45 minutes. The reaction was evaporated to dryness and the residue dissolved in DCM and poured onto an isolute SCX-2 ion exchange column. The column was eluted with methanol to elute any neutrals, followed by 7M methanolic ammonia to elute the product. The product containing fractions were evaporated to give S-2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidine (125mg, 15%) as an orange solid; NMR Spectrum 1.78 (m, 3H), 2.14 (m, 1H), 2.92 (t, 2H), 4.36 (t, 1H), 6.82 (s, 1H), 7.60 (t, 1H), 8.96 (d, 2H); Mass Spectrum 217 [MH]+.

Example 11

S-6-Methyl-2-{2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine

A mixture of the 2-chloro-6-methyl-4-(pyrid-2-ylamino)pyrimidine (148mg, 0.67mmol), S-2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidine (270mg, 1.25mmol) and N,N-diisopropylethylamine (0.35ml, 2.0mmol) in n-hexanol (10ml) was heated at 130°C, under nitrogen for 18 hours. The mixture was allowed to cool and the hexanol removed by pouring mixture on to an SCX2 ion exchange column and eluting with methanol. The product was eluted with 7M methanolic ammonia. The volatiles were removed by evaporation and the residue purified by column chromatography on silica gel, eluting with EtOAc / isohexane (40:60) to give the title compound; (95mg, 36%); NMR Spectrum 2.07-2.13 (m, 3H), 2.20 (s, 3H), 2.35-2.45 (m, 1H), 3.80-3.85 (m, 1H), 3.85-3.95 (m, 1H), 5.48 (d, 1H), 6.53 (s, 1H), 6.72 (d, 1H), 6.89-6.92 (m, 1H), 7.54 (t, 1H), 7.62 (t, 1H), 7.87 (d, 1H), 8.21-8.23 (m, 1H), 8.91 (d, 1H), 9.19 (s, 1H); Mass Spectrum 401 [MH]+

Example 12

S-6-Methyl-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(4-methylpyrid-2-ylamino)pyrimidine

A mixture of S-4-chloro-6-methyl-2-{2-[3-(pyridin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine (200mg, 0.58mmol), 2-amino-4-methylpyridine (54mg, 0.5mmol), cesium carbonate (230mg, 0.7mmol) in 1,4-dioxane (4ml) was purged with nitrogen for 10 minutes. Tris(dibenzylideneacetone)dipalladium(0) (25mg, 0.027mmol), 9,9-dimethyl-4,5-

bis(diphenylphosphino)xanthene (25mg, 0.043mmol) were added and the mixture stirred and heated at 100°C for 18 hours. The mixture was allowed to cool, insoluble material removed by filtration and the residue washed with DCM. The combined filtrates were poured onto a 20g SCX ion exchange column, and eluted with methanol to remove neutral impurities. The column was then eluted with 2M methanolic ammonia, the fractions containing product combined and the volatiles removed by evaporation. The residue was purified by reverse phase HPLC using a C18 column eluting with water / aqueous ammonia / acetonitrile (99:1:0 decreasing in polarity to 0:1:99). The purified product was triturated with DCM/hexane (1:10) to give the title compound (112mg, 54%) as a white solid; NMR Spectrum (398K) 2.00-2.10 (m, 2H), 2.10-2.20 (m, 1H), 2.18 (s, 3H), 2.25 (s, 3H), 2.30-2.45 (m, 1H), 3.65-3.85 (m, 2H), 5.45-5.55 (d, 1H), 6.50 (s, 1H), 6.65 (s, 1H), 6.70-6.75 (d, 1H), 7.4-7.45 (t, 1H), 7.80 (s, 1H), 7.85-7.95 (m, 2H), 8.02-8.08 (d, 1H), 8.60-8.65 (d, 1H), 9.05-9.15 (br s, 1H); Mass Spectrum 414 [MH]+.

The S-4-chloro-6-methyl-2-{2-[3-(pyridin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine starting material was prepared as follows:

A mixture of 4-hydroxy-6-methyl-2-(methylthio)pyrimidine (8.13g, 52.1mmol) and S-2-[3-(pyridin-2-yl)isoxazol-5-yl]pyrrolidine (13.13g , 60.8mmol) was heated in a melt reaction at 170°C for 4 hours under nitrogen. The reaction mixture was allowed to cool and the crude product purified by column chromatography on silica gel eluting with methanol / EtOAc (5:95 increasing in polarity to10:90) to give S-4-hydroxy-6-methyl-2-{2-[3-(pyridin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine (12.2g, 71%) as a beige crystals; NMR Spectrum (400MHz, $CDCl_3$) 2.08 (s, 3H), 2.17-2.23 (m, 2H), 2.30 (t, 2H), 3.56-3.63 (m, 1H), 3.89-3.94 (m, 1H), 5.63 (m, 2H), 6.71 (s, 1H), 7.31-7.35 (m, 1H), 7.76-7.80 (m, 1H), 8.04 (d, 1H), 8.64 (d, 1H), 11.60 (s, 1H); Mass Spectrum 324 [MH]+.

A solution of S-4-hydroxy-6-methyl-2-{2-[3-(pyridin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine (11.5g, 35.6mmol) in phosphorous (III) oxychloride (200ml) was heated at 85°C nitrogen for 1 hour. Excess phosphorous (III) oxychloride was removed by evaporation, and the residue was carefully treated with saturated aqueous potassium carbonate solution to adjust the resulting aqueous mixture to pH9. The mixture was extracted with EtOAc (4 x 150ml), the extracts dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography on silica gel eluting with EtOAc / isohexane (25:75) to give 4-chloro-6-methyl-2-{2-[3-(pyridin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine (11.35g, 93%) as a pale yellow viscous oil; NMR Spectrum

(400MHz, $CDCl_3$) 2.08-2.18 (m, 2H), 2.21 (m, 1H), 2.30-2.32 (m, 1H), 2.28-2.37 (m, 3H), 3.60-3.70 (m, 1H), 3.84-3.90 (m, 1H), 5.53 (t, 1H), 6.44 (s, 1H), 6.64 (s, 1H), 7.31-7.34 (m, 1H), 7.76-7.80 (m, 1H), 8.04-8.07 (m, 1H), 8.64-8.65 (m, 1H); Mass Spectrum 342 [MH]+.

Example 13

S-6-Methyl-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(5-methylpyrid-2-ylamino)pyrimidine

A mixture of S-4-chloro-6-methyl-2-{2-[3-(pyridin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine (200mg, 0.58mmol), 2-amino-5-methylpyridine (54mg, 0.5mmol), cesium carbonate (230mg, 0.7mmol) in 1,4-dioxane (4ml) was purged with nitrogen for 10 minutes. Tris(dibenzylideneacetone)dipalladium(0) (25mg, 0.027mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (25mg, 0.043mmol) were added and the mixture stirred and heated at 100°C for 18 hours. The mixture was allowed to cool, insoluble material removed by filtration and the residue washed with DCM. The combined filtrates were poured onto a 20g SCX ion exchange column, and eluted with methanol to remove neutral impurities. The column was then eluted with 2M methanolic ammonia, the fractions containing product combined and the volatiles removed by evaporation. The residue was purified by reverse phase HPLC using a C18 column eluting with water / aqueous ammonia / acetonitrile (99:1:0 decreasing in polarity to 0:1:99). The purified product was triturated with DCM/hexane (1:10) to give the title compound (111mg, 54%); NMR Spectrum (398K) 2.00-2.10 (m, 2H), 2.10-2.20 (m, 1H), 2.17 (s, 3H), 2.20 (s, 3H), 2.30-2.45 (m, 1H), 3.65-3.75 (m, 1H), 3.75-3.85 (m, 1H), 5.42-5.48 (d, 1H), 6.45 (s, 1H), 6.65 (s, 1H), 7.40-7.45 (m, 2H), 7.70-7.78 (d, 1H), 7.85-7.95 (m, 2H), 8.05-8.08 (br s, 1H), 8.60-8.65 (d, 1H), 9.05-9.10 (br s, 1H); Mass Spectrum 414 [MH]+.

Example 14

S-6-Methyl-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(5-cyanopyrid-2-ylamino)pyrimidine

Tris(dibenzylideneacetone)dipalladium(0) (20mg, 0.022mmol), and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (20mg, 0.034mmol) were added to a mixture of 2-amino-5-cyanopyridine (60mg, 0.5mmol), S-4-chloro-6-methyl-2-{2-[3-(pyridin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine (188mg, 0.55mmol) and cesium carbonate (326mg, 1.0mmol) in 1,4-dioxane (4ml) under nitrogen and the reaction mixture heated at 60°C under nitrogen

for 18 hours. The mixture was allowed to cool, the insoluble material removed by filtration, the solvent was removed from the filtrate by evaporation. The residue was purified by column chromatography on silica gel eluting with EtOAc / DCM (10:90) to give the title compound (33mg, 16%) as a white solid; NMR Spectrum 2.05-2.20 (m, 3H), 2.22 (s, 3H), 2.32-2.47 (m, 1H), 3.68-3.78 (m, 1H), 3.78-3.88 (m, 1H), 5.45-5.50 (d, 1H), 6.56 (s, 1H), 6.70 (s, 1H), 7.40-7.47 (m, 1H), 7.85-7.90 (m, 1H), 7.90-8.00 (m, 2H), 8.00-8.07 (d, 1H), 8.57 (s, 1H), 8.62-8.66 (d, 1H), 9.85(s, 1H). Mass Spectrum 425 [MH]+.

Example 15

S-6-Methyl-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(4-cyanopyrid-2-ylamino)pyrimidine

Tris(dibenzylideneacetone)dipalladium(0) (20mg, 0.022mmol), and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (20mg, 0.034mmol) were added to a mixture of 2-amino-4-cyanopyridine (60mg, 0.5mmol), S-4-chloro-6-methyl-2-{2-[3-(pyridin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine (188mg, 0.55mmol) and cesium carbonate (326mg, 1.0mmol) in 1,4-dioxane (4ml) under nitrogen and the reaction mixture heated at 60°C under nitrogen for 18 hours. The mixture was allowed to cool, the insoluble material removed by filtration, the solvent was removed from the filtrate by evaporation. The residue was purified by column chromatography on silica gel eluting with EtOAc / DCM (25:75) to give the title compound (140mg, 66%) as a white solid; NMR Spectrum 1.95-2.32 (m, 6H), 2.32-2.47 (m, 1H), 3.55-3.75 (m, 1H), 3.75-3.95 (m, 1H), 5.47-5.51 (d, 1H), 6.46 (s, 1H), 6.70 (s, 1H), 7.32 (br s, 1H), 7.42-7.54 (t, 1H), 7.70-8.05 (m, 2H), 8.20-8.55 (br m, 2H), 10.12 (br s1H); Mass Spectrum 425 [MH]+.

Example 16

S-6-Methyl-2-{2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(5-cyanopyrid-2-ylamino)pyrimidine

A mixture of the 2-chloro-6-methyl-4-(5-cyanopyrid-2-ylamino)pyrimidine (120mg, 0.49mmol), S-2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidine (158mg, 0.69mmol) and N,N-diisopropylethylamine (0.26ml, 1.48mmol) in n-hexanol (10ml) was heated at 130°C, under nitrogen for 18 hours. The solvent was then removed by evaporation and the residue purified by reverse phase HPLC using a C18 column eluting with water / acetonitrile / TFA (75:25:0.2 decreasing in polarity to 50:50:0.2). The product containing fractions were

combined, the organic solvent was removed by evaporation and aqueous residue treated with saturated aqueous sodium hydrogen carbonate solution. The resulting solid precipitate was collected by filtration and dried to give the title compound (125mg, 58%); NMR Spectrum 2.0-2.2 (m, 4H), 2.23 (s, 3H), 2.75 (s, 3H), 3.30-3.76 (m, 1H), 3.80-3.91 (m, 1H), 5.50 (d, 1H), 6.58 (s, 1H), 6.73 (s, 1H), 7.96 (d, 1H), 8.03 (d, 1H), 8.57 (dd, 3H), 9.84 (s, 1H); Mass Spectrum 440 [MH]+.

The 2-chloro-6-methyl-4-(5-cyanopyrid-2-ylamino)pyrimidine starting material was prepared as follows:

A mixture of 2,4-dichloro-6-methylpyrimidine (2.0g, 12.3mmol), 2-amino-5-cyanopyridine (1.1g, 9.48mmol) and cesium carbonate (4.3g, 13.2mmol) in 1,4-dioxane (20ml) was purged with nitrogen for 10 minutes. 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (470mg, 0.8mmol), tris(dibenzylideneacetone) dipalladium(0) (470mg, 0.53mmol) were added and heated to 100°C for 8 hours. The mixture was allowed to cool, filtered through diatomeous earth the filter pad washed with methanol and the solvent removed from the filtrate by evaporation. The residue was dissolved in EtOAc, washed with water and dried (Na_2SO_4) and the solvent removed by evaporation. The residue was purified by column chromatography on silica gel eluting with EtOAc / isohexane (40:60) to give 2-chloro-6-methyl-4-(5-cyanopyrid-2-ylamino)pyrimidine (370mg,10%); NMR Spectrum 2.41 (s, 3H), 7.67 (d, 1H), 7.74 (s, 1H), 8.22 (dd, 1H), 8.79 (d, 1H), 11.06 (s, 1H); Mass Spectrum 245 [MH]+.

Example 17

S-6-Methoxy-2-{2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine

A mixture of S-4-chloro-6-methoxy-2-{2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine (180mg, 0.46mmol), 2-aminopyridine (91mg, 0.97mmol), cesium carbonate (230mg, 0.71mmol), in 1,4-dioxane (4ml) were purged with nitrogen for 10 minutes. Tris(dibenzylideneacetone)dipalladium(0) (25mg, 0.027mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (25mg, 0.043mmol) and were added, the mixture purged with nitrogen for 1 minute and the reaction vessel was sealed.. The mixture was heated at 150°C under microwave irradiation for 2 hours. The mixture was allowed to cool, the solvent removed by evaporation, the residue was partitioned between EtOAc and water, the organic layer separated, dried (Na_2SO_4) and the solvent removed by evaporation. The residue

was purified by reverse phase HPLC using a C18 column eluting with water / acetonitrile / TFA (70:20:0.2 decreasing in polarity to 50:50:0.2). The product containing fractions were combined, the organic solvent was removed by evaporation and aqueous residue treated with saturated aqueous sodium hydrogen carbonate solution. The resulting solid precipitate was collected by filtration, washed with ether/hexane and dried to give the title compound (6mg, 3%); NMR Spectrum 2.09-2.14 (m, 3H), 2.42-2.45 (m, 1H), 3.73-3.79 (m, 2H), 3.76 (s, 3H), 4.01 (s, 3H), 5.47 (d, 1H), 6.20 (s, 1H), 6.71 (s, 1H), 6.88-6.91 (m, 1H), 7.60-7.62 (m, 1H), 7.79 (d, 1H), 8.21 (d, 1H), 8.31 (s, 2H), 9.11 (s, 1H); Mass Spectrum 447 [MH]+.

The S-4-chloro-6-methoxy-2-{2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine starting material was prepared as follows:

A mixture of barbituric acid (19.5g, 0.152mol) and boron trifluoride etherate (75ml) in methanol (300ml) was heated and the ether removed by distillation. The mixture was then heated under reflux for 3 hours. The mixture was then cooled in an ice bath, solid material was collected by filtration and washed through with water. The solid was suspended in water heated to 100°C, allowed to cool and collected by filtration, washed with acetone/water and dried to give 2,4-dihydroxy-6-methoxypyrimidine (14.5g, 67%); NMR Spectrum 3.78 (s, 3H), 4.93-4.94 (m, 1H), 10.67 (s, 1H), 11.26 (s, 1H).

A mixture of 2,4-dihydroxy-6-methoxypyrimidine (15g, 0.106mol) in phosphorus (III) oxychloride (400ml) was heated under reflux for 4 hours to give solution. Excess phosphorus (III) oxychloride was removed by evaporation, the residue treated with ice/water and extracted with EtOAc. The combined extracts were washed with water, dried (Na_2SO_4) . and the solvent removed by evaporation to give 2,4-dichloro-6-methoxypyrimidine (5.5g, 30%) as an oil; NMR Spectrum 3.96 (s, 3H), 6.63 (s, 1H); Mass Spectrum 179 [MH]+

A mixture of 2,4-dichloro-6-methoxypyrimidine (200mg, 1.12mmol), S-2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidine (described in Example 5) (246mg, 1.0mmol), Zinc (II) acetate (159mg, 1.0mmol) in isopropanol (10ml) was heated at 100°C for 18 hours. The solvent was removed by evaporation and the residue partitioned between aqueous ammonium chloride solution and DCM. The organic phase was separated, the solvent removed by evaporation and the residue purified by column chromatography on silica gel eluting with EtOAc / isohexane (25:75) to give S-4-chloro-6-methoxy-2-{2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine (188mg, 43%); Mass Spectrum 390 [MH]+.

Example 18

S-6-Methoxy-2-{2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine

A mixture of S-4-chloro-6-methoxy-2-{2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine (160mg, 0.43mmol), 2-aminopyridine (94mg, 1.0mmol), cesium carbonate (230mg, 0.71mmol), in 1,4-dioxane (4ml) were purged with nitrogen for 10 minutes. Tris(dibenzylideneacetone)dipalladium(0) (10mg, 0.011mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (10mg, 0.017mmol) and were added, the mixture purged with nitrogen for 1 minute and the reaction vessel was sealed. The mixture was heated at 100°C under microwave irradiation for 18 hours. The mixture was allowed to cool, more 2-aminopyridine (94mg, 1.0mmol), tris(dibenzylideneacetone)dipalladium(0) (10mg, 0.011mmol) and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (10mg, 0.017mmol) were added, the mixture purged with nitrogen for 1 minute and then heated at 100°C for 2 hours and then at 150°C for 90 minutes under microwave irradiation. The mixture was allowed to cool, insoluble material removed by filtration and the solvent removed from the filtrate by evaporation. The residue was purified by column chromatography on silica gel eluting with EtOAc / isohexane (0:100 increasing in polarity to 40:60) and the purified product triturated with DCM / hexane (1:10) to give the title compound (39mg, 21%) as beige solid; NMR spectrum (373K) 2.04-2.20 (m, 3H), 2.4-2.5 (m, 1H), 2.75 (s, 3H), 3.70-3.80 (m, 1H), 3.78 (s, 3H), 3.78-3.88 (m, 1H), 5.40-5.50 (d, 1H), 6.18 (s, 1H), 6.70 (s, 1H), 6.85-6.90 (m, 1H), 7.55-7.65 (m, 1H), 7.75-7.80 (m, 1H), 8.15-8.20 (d, 1H), 8.50-8.58 (m, 2H), 9.05-9.10 (br s, 1H); Mass Spectrum 431 [MH]+.

The S-4-chloro-6-methoxy-2-{2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine starting material was prepared as follows:

A mixture of 2,4-dichloro-6-methoxypyrimidine (260mg, 1.5mmol), S-2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidine (230mg, 1.0mmol) and zinc (II) acetate (185mg, 1.0mmol) in isopropanol (7ml) were heated under reflux for 18 hours. The solution was allowed to cool and solvent removed by evaporation. The residue was partitioned between aqueous ammonium chloride solution and DCM. The organic phase was separated, and the aqueous phase extracted with DCM. The extracts were combined, washed with water and then brine, dried (Na_2SO_4) and the solvent removed by evaporation. The residue was purified by column chromatography on silica gel eluting with EtOAc / isohexane (10:90 increasing in polarity to 25:75) to give S-4-chloro-6-methoxy-2-{2-[3-(3-methylpyrazin-2-

yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine (160mg, 43%); NMR spectrum (373K) 2.04-2.20 (m, 3H), 2.40-2.50 (m, 1H), 2.75 (s, 3H), 3.65-3.75 (m, 1H), 3.75-3.85 (m, 1H), 3.82 (s, 3H), 5.40-5.48 (d, 1H), 6.15 (s, 1H), 6.75 (s, 1H), 8.55-8.60 (m, 2H); Mass Spectrum 373 [MH]+.

Example 19

S-6-Methoxy-2-{2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine

A mixture of S-4-chloro-6-methoxy-2-{2-[3-(pyrimidin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine (90mg, 0.25mmol), 2-amino pyridine (28mg, 0.3mmol) and cesium carbonate (163mg, 0.5mmol) in 1,4-dioxane (4ml) were purged with nitrogen for 10 minutes. Tris(dibenzylideneacetone)dipalladium(0) (23mg, 0.025mmol), 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (22mg, 0.038mmol) and were added, the mixture purged with nitrogen for a further 5 minutes then heated at 80°C for 16 hours. Further 2-amino pyridine (7mg, 0.07mmol), tris(dibenzylideneacetone)dipalladium(0) (12 mg, 0.013mmol) and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (14mg, 0.024mmol) were added, the mixture purged with nitrogen for 1 minute and then heated at 80°C for 5 hours and then at 150°C under microwave irradiation for 90 minutes. The mixture was allowed to cool, insoluble material removed by filtration and the solvent removed from the filtrate by evaporation. The residue was purified by column chromatography on silica gel eluting with a gradient of methanol / DCM (0:100 increasing in polarity to 5:95). The purified product was then re-purified by column chromatography on silica gel eluting with a gradient of EtOAc / isohexane (50:50 increasing in polarity to 65:35). The purified product was triturated with dichloromethane / isohexane (1:9), collected by filtration and dried to give the title compound (20 mg, 19 %) as a white solid; NMR spectrum 2.12 (m, 3H), 2.42 (m, 1H), 3.74 (m, 4H), 3.82 (m, 1H), 5.45 (m, 1H), 6.18 (s, 1H), 6.74 (s, 1H), 6.86 (m, 1H), 7.52 (m, 1H), 7.59 (m, 1H), 7.75 (m, 1H), 8.18 (m, 1H), 8.90 (m, 2H), 9.06 (s, 1H); Mass Spectrum 417 [MH]+.

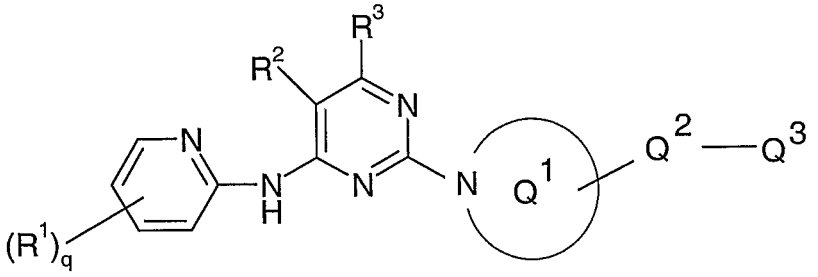
The S-4-chloro-6-methoxy-2-{2-[3-(pyrimidin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine starting material was prepared as follows:

A mixture of 2,4-dichloro-6-methoxypyrimidine (260mg, 1.50mmole), S-2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidine (238mg, 1.10mmole) and zinc (II) acetate (159mg, 1.0mmole) in isopropanol (4ml) were heated under reflux for 18 hours. The solution was cooled and solvent removed by evaporation. The residue was partitioned between aqueous ammonium chloride solution and DCM. The organic phase was separated, and the aqueous

phase extracted with DCM. The extracts were combined, washed with water and then brine, dried (Na_2SO_4) and the solvent removed by evaporation. The residue was purified by column chromatography on silica gel eluting with EtOAc / isohexane (10:90 increasing in polarity to 25:75) to give S-4-chloro-6-methoxy-2-{2-[3-(pyrimidin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}pyrimidine as an oil (184mg, 43%) NMR spectrum (373K) 2.04-2.20 (m, 3H), 2.40-2.50 (m, 1H), 2.90 (s, 3H), 3.65-3.75 (m, 1H), 3.75-3.81 (m, 1H), 3.80 (s, 3H), 5.44 (d, 1H), 6.14 (s, 1H), 6.77 (s, 1H), 7.54 (t, 1H), 8.92 (d, 2H); Mass Spectrum 357 [MH]+.

CLAIMS

1. A compound of formula (I):



(I)

wherein:

R^1 is selected from cyano, or from a (C1-C6)alkyl, amino, (C1-C4)alkylamino, di-[(C1-C4)alkyl]amino, carbamoyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl or $-N(R^{1a})C(O)R^{1b}$ group, wherein R^{1a} and R^{1b} are each independently selected from hydrogen and (C1-C6)alkyl, each of which groups may be optionally substituted by one or more substituents independently selected from halogeno and (C1-C6)alkoxy;

q is 0, 1, 2 or 3;

R^2 is selected from hydrogen, halogeno and trifluoromethyl;

R^3 is selected from hydrogen, hydroxy and halogeno, or from a (C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl, (C1-C6)alkoxy, (C3-C8)cycloalkyl(C1-C6)alkoxy, (C1-C6)alkylcarbonyl, (C3-C8)cycloalkylcarbonyl, (C3-C8)cycloalkyl(C1-C6)alkylcarbonyl, (C1-C6)alkoxycarbonyl, amino, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, (C3-C8)cycloalkylamino, (C3-C8)cycloalkyl(C1-C6)alkylamino, (C1-C6)alkoxyamino, carbamoyl, (C1-C6)alkylcarbamoyl, di-[(C1-C6)alkyl]carbamoyl, $-C(O)R^{3b}$, $-OR^{3b}$, $-SR^{3b}$, $-NHR^{3b}$, $-N[(C1-C6)alkyl]R^{3b}$, $-S(O)_mR^{3a}$ or $-N(R^{3c})C(O)R^{3a}$ group, wherein m is 0, 1 or 2, R^{3a} is selected from a (C1-C6)alkyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl or (C1-C6)alkoxy group, R^{3b} is a saturated monocyclic 4-, 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur and R^{3c} is selected from hydrogen and (C1-C6)alkyl,

or R^3 is a saturated monocyclic 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur,

or R^3 is a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur,

or R^3 is a 2,7-diazaspiro[3.5]nonane group,

each of which groups or rings within R^3 may be optionally substituted by one or more substituents independently selected from (C1-C6)alkyl, (C1-C6)alkoxy, (C1-C6)alkoxy(C1-C6)alkyl, (C1-C6)alkoxy(C1-C6)alkoxy, halogen, hydroxy, trifluoromethyl, tri-[(C1-C4)alkyl]silyl, cyano, amino, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, (C3-C8)cycloalkylamino, (C3-C6)cycloalkyl(C1-C3)alkylamino, amino(C1-C6)alkyl, (C1-C6)alkylamino(C1-C6)alkyl, di-[(C1-C6)alkyl]amino(C1-C6)alkyl, (C3-C8)cycloalkylamino(C1-C6)alkyl, (C3-C6)cycloalkyl(C1-C3)alkylamino(C1-C6)alkyl, (C1-C6)alkoxycarbonyl, carbamoyl, (C1-C6)alkylcarbamoyl, di-[(C1-C6)alkyl]carbamoyl, (C1-C6)alkylthio, (C1-C6)alkylsulfonyl, (C1-C6)alkylsulfinyl, (C1-C6)alkanoyl, an alkanoylamino group $-N(R^{3d})C(O)R^{3e}$ wherein R^{3d} is selected from hydrogen and (C1-C6)alkyl and R^{3e} is selected from a (C1-C6)alkyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl or (C1-C6)alkoxy group, or a saturated monocyclic 3-, 4-, 5-, 6- or 7-membered ring, which ring may optionally comprise one or more heteroatoms selected from nitrogen, oxygen and sulfur, any of which substituents may be optionally substituted by one or more (C1-C4)alkyl, hydroxy or cyano groups;

$-NQ^1$ is a N-linked azetidinyl or pyrrolidinyl ring;

Q^2 is a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur, which ring is substituted by Q^3 and is optionally substituted, on any available ring atom, by one or more further substituents independently selected from (C1-C6)alkyl and (C1-C6)alkoxy (either of which (C1-C6)alkyl and (C1-C6)alkoxy substituent groups may be optionally substituted by one or more substituents independently selected from halogeno, amino, hydroxy and trifluoromethyl), halogeno, nitro, cyano, $-NR^4R^5$, carboxy, hydroxy, (C2-C6)alkenyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkyl(C1-C6)alkyl, (C1-C4)alkoxycarbonyl, (C1-C4)alkylcarbonyl, (C2-C6)alkanoylamino, phenylcarbonyl, $-S(O)_p$(C1-C4)alkyl, $-C(O)NR^6R^7$ and $-SO_2NR^8R^9$, wherein R^4, R^5, R^6, R^7, R^8 and R^9 are each independently selected from hydrogen and (C1-C6)alkyl, or R^4 and R^5, or R^6 and R^7, or R^8 and R^9, when taken together with the nitrogen atom to which they are attached, may each independently form a saturated heterocyclic ring and p is 0, 1 or 2;

Q^3 is selected from a (C1-C6)alkyl, (C3-C6)cycloalkyl or (C3-C6)cycloalkyl(C1-C6)alkyl group or a saturated or unsaturated 5- or 6-membered monocyclic ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulfur, and wherein

Q^3 is optionally substituted by one or more substituents independently selected from (C1-C6)alkyl and (C1-C6)alkoxy (either of which (C1-C6)alkyl and (C1-C6)alkoxy substituent groups may be optionally substituted by one or more substituents independently selected from halogeno, amino, hydroxy and trifluoromethyl), halogeno, nitro, cyano, $-NR^{10}R^{11}$, carboxy, hydroxy, (C2-C6)alkenyl, (C3-C8)cycloalkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C2-C6)alkanoylamino, phenylcarbonyl, $-S(O)_n$(C1-C6)alkyl, $-C(O)NR^{12}R^{13}$ and $-SO_2NR^{14}R^{15}$, wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are each independently selected from hydrogen and (C1-C6)alkyl, or R^{10} and R^{11}, or R^{12} and R^{13}, or R^{14} and R^{15}, when taken together with the nitrogen atom to which they are attached, may each independently form a saturated heterocyclic ring and n is 0, 1 or 2;

and wherein any saturated monocyclic ring optionally bears 1 or 2 oxo or thioxo substituents;

or a pharmaceutically-acceptable salt thereof.

2. A compound of formula (I) according to claim 1, wherein R^1 is selected from (C1-C2)alkyl and cyano.

3. A compound of formula (I) according to claim 1 or 2, wherein q is 0 or 1.

4. A compound of formula (I) according to any one or more of claims 1 to 3, wherein R^2 is hydrogen.

5. A compound of formula (I) according to any one or more of claims 1 to 4, wherein R^3 is selected from hydrogen, hydroxy or halogeno, or from a (C1-C4)alkyl, (C2-C4)alkenyl, (C2-C4)alkynyl, (C1-C3)alkoxy, amino, (C1-C3)alkylamino, di-[(C1-C3)alkyl]amino, (C3-C6)cycloalkylamino, carbamoyl, (C1-C3)alkylcarbamoyl, di-[(C1-C3)alkyl]carbamoyl, $-C(O)R^{3b}$, $-OR^{3b}$, $-NHR^{3b}$ or $-S(O)_mR^{3a}$ group, wherein R^{3a} is a (C1-C3)alkyl group, m is 0 and R^{3b} is a saturated monocyclic 4-, 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulfur,

or R^3 is a saturated monocyclic 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen and oxygen,

or R^3 is a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen and oxygen,

each of which groups or rings within R^3 may be optionally substituted by one or more substituents independently selected from (C1-C3)alkyl, (C1-C3)alkoxy, (C1-C3)alkoxy(C1-C3)alkyl, (C1-C3)alkoxy(C1-C3)alkoxy, halogeno, hydroxy, trifluoromethyl, amino, (C1-C3)alkylamino, di-[(C1-C3)alkyl]amino, amino(C1-C3)alkyl, carbamoyl, (C1-C3)alkylcarbamoyl, (C1-C3)alkylthio, (C1-C3)alkylsulfonyl, (C1-C3)alkanoyl, an alkanoylamino group $-N(R^{3d})C(O)R^{3e}$ wherein R^{3d} is selected from hydrogen and (C1-C3)alkyl and R^{3e} is selected from a (C1-C3)alkyl or (C1-C3)alkoxy group, or a saturated monocyclic 3-, 4-, 5- or 6-membered ring, which ring may optionally comprise one or more heteroatoms selected from nitrogen, oxygen and sulfur, any of which substituents may be optionally substituted by one or more (C1-C2)alkyl, hydroxy or cyano groups,

and wherein any saturated monocyclic ring within R^3 optionally bears 1 oxo substituent.

6. A compound of formula (I) according to any one or more of claims 1 to 5, wherein R^3 is selected from halogeno, or from a (C1-C4)alkyl or (C1-C3)alkoxy group, or R^3 is a saturated monocyclic 5- or 6-membered heterocyclic ring comprising at least one ring heteroatom selected from nitrogen and oxygen,

each of which groups or rings within R^3 may be optionally substituted by one or more substituents independently selected from hydroxy and (C1-C3)alkoxy.

7. A compound of formula (I) according to any one or more of claims 1 to 6, wherein R^3 is selected from chloro, methyl, ethyl, methoxy and morpholino.

8. A compound of formula (I) according to any one or more of claims 1 to 7, wherein $-NQ^1$ is a N-linked pyrrolidinyl group.

9. A compound of formula (I) according to any one or more of claims 1 to 8, wherein Q^2 is selected from thienyl, pyrazolyl, oxazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, triazolyl, tetrazolyl, imidazolyl, pyrazinyl, pyridazinyl, pyrimidinyl and pyridyl.

10. A compound of formula (I) according to claim 9, wherein Q^2 is isoxazolyl.

11. A compound of formula (I) according to any one or more of claims 1 to 10, wherein Q^3 is an unsaturated 5- or 6-membered monocyclic ring comprising one or two ring heteroatoms, which may be the same or different, selected from nitrogen, oxygen and sulfur,

wherein Q^3 is optionally substituted by one or more substituents independently selected from (C1-C6)alkyl and (C1-C6)alkoxy (either of which (C1-C6)alkyl and (C1-C6)alkoxy substituent groups may be optionally substituted by one or more substituents independently selected from halogeno, amino, hydroxy and trifluoromethyl), halogeno, nitro, cyano, $-NR^{10}R^{11}$, carboxy, hydroxy, (C2-C6)alkenyl, (C3-C8)cycloalkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C2-C6)alkanoylamino, phenylcarbonyl, $-S(O)_n$(C1-C6)alkyl, $-C(O)NR^{12}R^{13}$ and $-SO_2NR^{14}R^{15}$, wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are each independently selected from hydrogen and (C1-C6)alkyl, or R^{10} and R^{11}, or R^{12} and R^{13}, or R^{14} and R^{15}, when taken together with the nitrogen atom to which they are attached, may each independently form a saturated heterocyclic ring and n is 0, 1 or 2;

and wherein any saturated monocyclic ring optionally bears 1 or 2 oxo or thioxo substituents.

12. A compound of formula (I) according to any one or more of claims 1 to 11, wherein Q^3 is selected from pyrazinyl, pyrimidinyl, pyridyl and thiazolyl,

wherein Q^3 is optionally substituted by one or more substituents independently selected from (C1-C6)alkyl and (C1-C6)alkoxy (either of which (C1-C6)alkyl and (C1-C6)alkoxy substituent groups may be optionally substituted by one or more substituents independently selected from halogeno, amino, hydroxy and trifluoromethyl), halogeno, nitro, cyano, $-NR^{10}R^{11}$, carboxy, hydroxy, (C2-C6)alkenyl, (C3-C8)cycloalkyl, (C1-C6)alkoxycarbonyl, (C1-C6)alkylcarbonyl, (C2-C6)alkanoylamino, phenylcarbonyl, $-S(O)_n$(C1-C6)alkyl, $-C(O)NR^{12}R^{13}$ and $-SO_2NR^{14}R^{15}$, wherein R^{10}, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are each independently selected from hydrogen and (C1-C6)alkyl, or R^{10} and R^{11}, or R^{12} and R^{13}, or R^{14} and R^{15}, when taken together with the nitrogen atom to which they are attached, may each independently form a saturated heterocyclic ring and n is 0, 1 or 2;

and wherein any saturated monocyclic ring optionally bears 1 or 2 oxo or thioxo substituents.

13. A compound of formula (I) according to claim 12, wherein Q^3 is selected from pyrazinyl, pyrimidinyl, pyridyl and thiazolyl,

wherein Q^3 is optionally substituted by one or more substituents independently selected from (C1-C4)alkyl, (C1-C4)alkoxy and cyano.

14. A compound of formula (I) selected from one or more of:

S-6-methyl-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-chloro-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-morpholino-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methoxy-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(thiazol-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-ethyl-2-{2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(2-cyanopyrid-3-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-ethyl-2-{2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(4-methylpyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(5-methylpyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(5-cyanopyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(pyrid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(4-cyanopyrid-2-ylamino)pyrimidine;

S-6-methyl-2-{2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(5-cyanopyrid-2-ylamino)pyrimidine;

S-6-methoxy-2-{2-[3-(3-methoxypyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

S-6-methoxy-2-{2-[3-(3-methylpyrazin-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine; and

S-6-methoxy-2-{2-[3-(pyrimid-2-yl)isoxazol-5-yl]pyrrolidin-1-yl}-4-(pyrid-2-ylamino)pyrimidine;

and pharmaceutically-acceptable salts thereof.

15. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically-acceptable salt thereof, according to any one or more of claims 1 to 14 in association with a pharmaceutically-acceptable adjuvant, diluent or carrier.

16. A pharmaceutical product which comprises a compound of formula (I), or a pharmaceutically-acceptable salt thereof, according to any one or more of claims 1 to 14 and an additional anti-tumour agent for the conjoint treatment of cancer.

17. A compound of formula (I), or a pharmaceutically-acceptable salt thereof, according to any one or more of claims 1 to 14 for use as a medicament.

18. Use of a compound of formula (I), or a pharmaceutically-acceptable salt thereof, according to any one or more of claims 1 to 14 in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal.

19. A method for producing an anti-proliferative effect in a warm-blooded animal 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, according to any one or more of claims 1 to 14.

20. Use of a compound of Formula (I), or a pharmaceutically-acceptable salt thereof, according to any one or more of claims 1 to 14 in the manufacture of a medicament for use in

the treatment of a disease or medical condition mediated alone or in part by IGF-1R tyrosine kinase in a warm-blooded animal.

21. A method for treating a disease or medical condition mediated alone or in part by IGF-1R tyrosine kinase in a warm-blooded animal 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, according to any one or more of claims 1 to 14.

22. Use of a compound of formula (I), or a pharmaceutically-acceptable salt thereof, according to any one or more of claims 1 to 14 in the manufacture of a medicament for use in the prevention or treatment of those tumours which are sensitive to inhibition of IGF-1R tyrosine kinase involved in the signal transduction steps which lead to the proliferation of tumour cells in a warm-blooded animal.

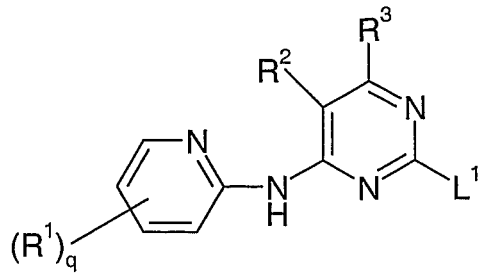
23. A method for the prevention or treatment of those tumours which are sensitive to inhibition of IGF-1R tyrosine kinase involved in the signal transduction steps which lead to the proliferation of tumour cells in a warm-blooded animal in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically-acceptable salt thereof, according to any one or more of claims 1 to 14.

24. Use of a compound of formula (I), or a pharmaceutically-acceptable salt thereof, according to any one or more of claims 1 to 14 in the manufacture of a medicament for the treatment of cancer in a warm-blooded animal.

25. A method for the treatment of cancer in a warm-blooded animal 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, according to any one or more of claims 1 to 14.

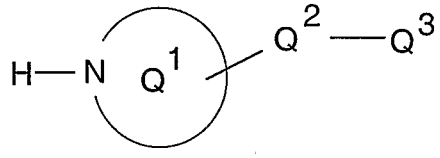
26. A process for the preparation of a compound of formula (I), or a pharmaceutically-acceptable salt thereof, according to claim 1 which comprises:

(a) the reaction, conveniently in the presence of a suitable base, of a compound of formula (II):



(II)

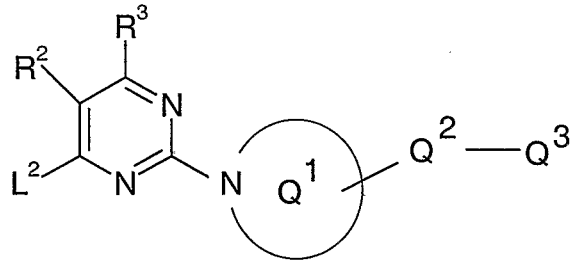
wherein L^1 represents a suitable displaceable group and q, R^1, R^2 and R^3 are as defined in claim 1 except that any functional group is protected if necessary, with a compound of formula (III):



(III)

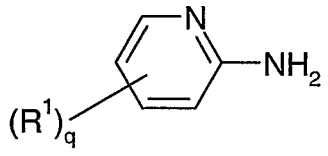
wherein $-NQ^1$, Q^2 and Q^3 are as defined in claim 1 except that any functional group is protected if necessary; or

(b) the reaction, conveniently in the presence of a suitable acid, of a compound of formula (IV):



(IV)

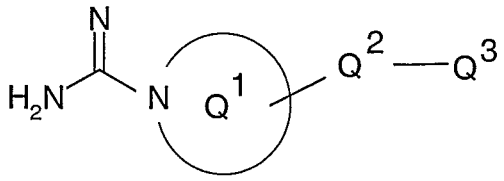
wherein L^2 is a suitable displaceable group and R^2, R^3, $-NQ^1$, Q^2 and Q^3 are as defined in claim 1 except that any functional group is protected if necessary, with an amino-pyridine of formula (V):



(V)

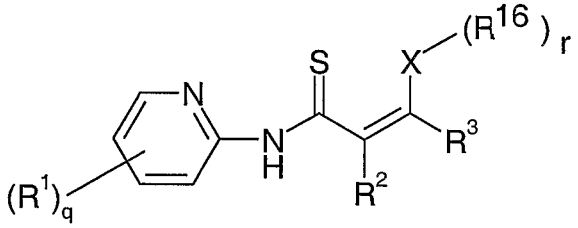
wherein q and R^1 are as defined in claim 1 except that any functional group is protected if necessary; or

Process (c) the reaction, conveniently in the presence of a suitable base, of a compound of formula (VI):



(VI)

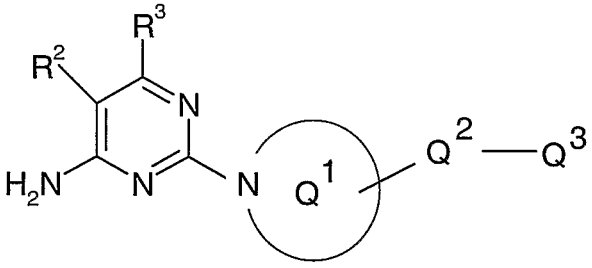
wherein $-NQ^1$, Q^2 and Q^3 are as defined in claim 1 except that any functional group is protected if necessary, with a compound of formula (VII):



(VII)

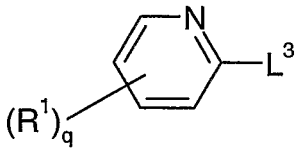
wherein X represents an oxygen atom and r is 1 or X represents a nitrogen atom and r is 2, R^{16} is a (C1-C6)alkyl group and q, R^1, R^2 and R^3 are as defined in claim 1 except that any functional group is protected if necessary; or

(d) the reaction of a compound of formula (VIII):



(VIII)

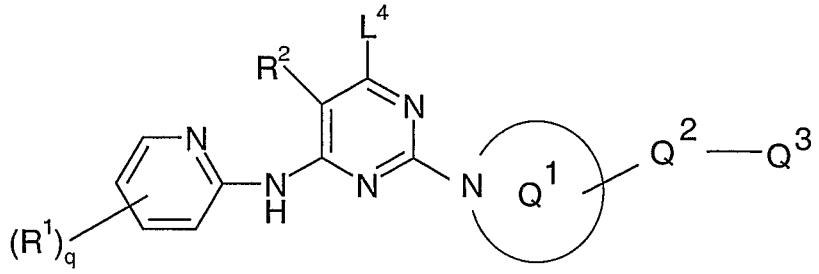
wherein $-NQ^1$, Q^2, Q^3, R^2 and R^3 are as defined in claim 1 except that any functional group is protected if necessary, with a compound of formula (IX):



(IX)

wherein L^3 is a suitable displaceable group and q and R^1 are as defined in claim 1 except that any functional group is protected if necessary; or

(e) for compounds of formula (I) wherein R^3 is a (C1-C6)alkoxy, amino, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, $-OR^{3b}$, $-SR^{3b}$, $-NHR^{3b}$, $-N[(C1-C6)alkyl]R^{3b}$ or $-S(O)_mR^{3a}$ group wherein m is 0 and R^{3a} and R^{3b} are as defined in claim 1 (and the group R^3 is optionally substituted by at least one group as defined in claim 1), the reaction, conveniently in the presence of a suitable base, of a compound of formula (X):



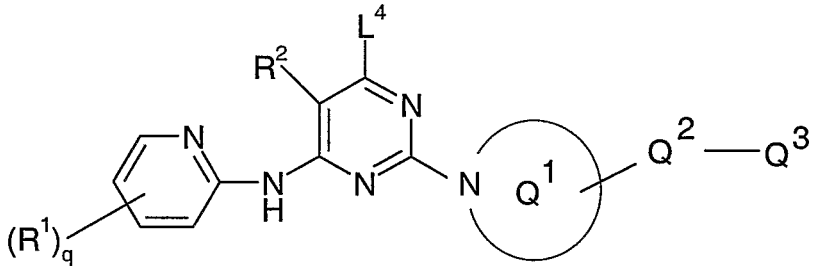
(X)

wherein L^4 is a suitable displaceable group and q, R^1, R^2, $-NQ^1$, Q^2 and Q^3 are as defined in claim 1 except that any functional group is protected if necessary, with a compound of formula:

H-Xa

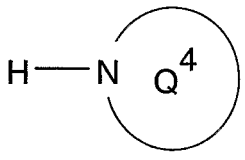
wherein Xa represents OR^{17}, NH_2, NHR^{17}, $N(R^{17})_2$, OR^{3b}, SR^{3b}, NHR^{3b}, N[(C1-C6)alkyl]R^{3b} and SR^{3a}, wherein R^{17} is an, optionally substituted, (C1-C6)alkyl group and R^{3a} and R^{3b} are each as defined in claim 1 except that any functional group is protected if necessary; or

(f) for compounds of formula (I) wherein R^3 is (i) an, optionally substituted, saturated monocyclic 5- or 6-membered heterocyclic ring comprising at least one ring nitrogen and, optionally, one or more additional heteroatoms selected from nitrogen, oxygen and sulfur, or (ii) an optionally substituted 2,7-diazaspiro[3.5]nonane group, the reaction, conveniently in the presence of a suitable base, of a compound of formula (X):



(X)

wherein L^4 is a suitable displaceable group and q, R^1, R^2, $-NQ^1$, Q^2 and Q^3 are as defined in claim 1 except that any functional group is protected if necessary, with (i) a compound of formula (Xb):

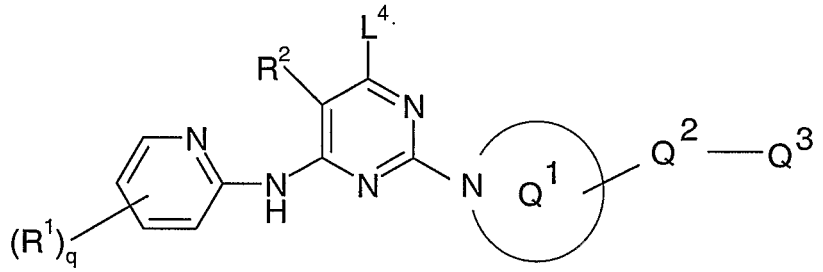


(Xb)

wherein Q^4 is a saturated monocyclic 5- or 6-membered heterocyclic ring optionally comprising one or more heteroatoms selected from nitrogen, oxygen and sulfur in addition to the nitrogen atom shown above, which ring is optionally substituted by at least one group as

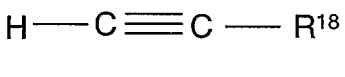
defined in claim 1, or with (ii) an optionally substituted 2,7-diazaspiro[3.5]nonane; or

(g) for compounds of formula (I) wherein R^3 is a (C2-C6)alkenyl or (C2-C6)alkynyl group, and the group R^3 is optionally substituted by at least one group as defined in claim 1, the reaction, conveniently in the presence of a suitable base and a suitable catalyst, of a compound of formula (X):

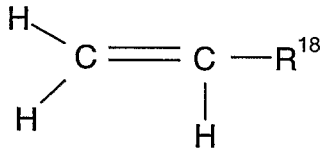


(X)

wherein L^4 is a suitable displaceable group and q, R^1, R^2, $-NQ^1$, Q^2 and Q^3 are as defined in claim 1 except that any functional group is protected if necessary, with a compound of formula (Xc) or of formula (Xc'):



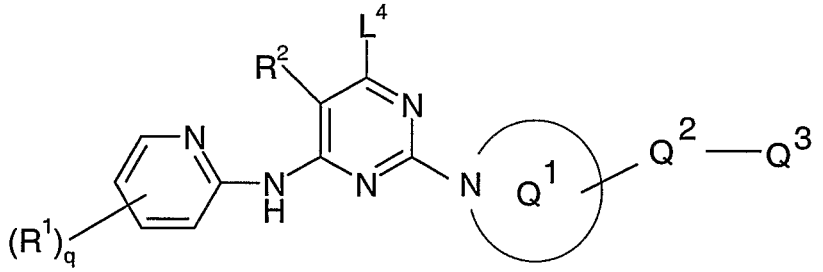
(Xc)



(Xc')

wherein R^{18} is selected from hydrogen and an, optionally substituted, (1-4C)alkyl or (C1-C4)alkoxycarbonyl group; or

(h) for compounds of formula (I) wherein R^3 is attached to the pyrimidine ring through a carbon atom, the reaction, conveniently in the presence of a suitable catalyst, of a compound of formula (X):



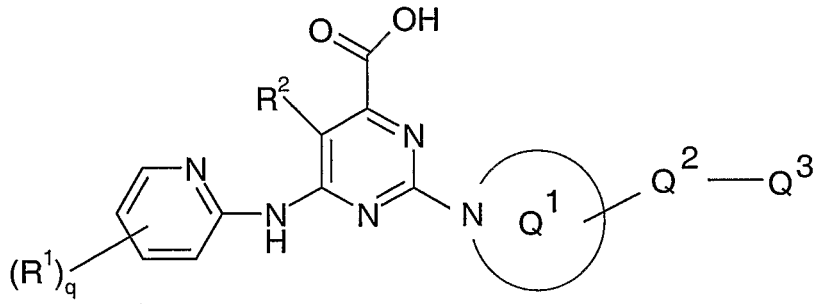
(X)

wherein L^4 is a suitable displaceable group and q, R^1, R^2, $-NQ^1$, Q^2 and Q^3 are as defined in claim 1 except that any functional group is protected if necessary, with a compound of the formula:

$M\text{-}R^3$

wherein R^3 is appropriately selected from the R^3 groups as defined in claim 1 and M is a metallic group; or

(i) for compounds of formula (I) wherein R^3 is a (C1-C6)alkoxycarbonyl group (and the group R^3 is optionally substituted by at least one group as defined in claim 1), the reaction, conveniently in the presence of a suitable acid, of a compound of formula (XI):



(XI)

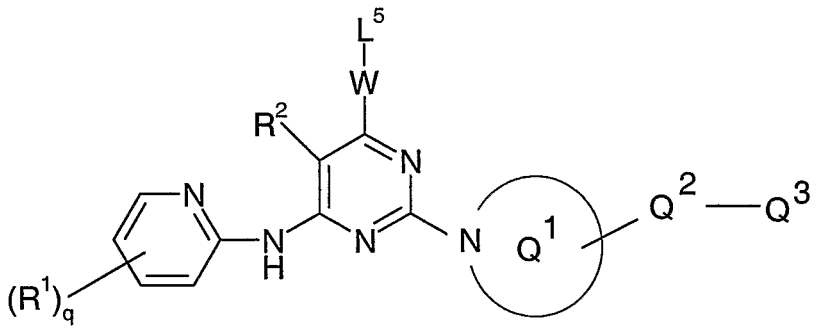
wherein q, R^1, R^2, $-NQ^1$, Q^2 and Q^3 are as defined in claim 1 except that any functional group is protected if necessary, with a compound of formula:

H-O-(C1-C6)alkyl

wherein the (C1-C6)alkyl group is optionally substituted by at least one group as defined in claim 1 as a substituent for R^3 and any functional group is protected if necessary; or

(j) for compounds of formula (I) wherein R^3 is a 5-membered heteroaromatic ring comprising at least one heteroatom selected from nitrogen, oxygen and sulfur (and the group R^3 is optionally substituted by at least one group as defined in claim 1), an internal condensation reaction using an appropriate starting material and a suitable dehydrating agent; or

(k) for compounds of formula (I) wherein R^3 is a (C1-C6)alkyl, (C3-C6)alkenyl, (C3-C6)alkynyl or (C1-C6)alkoxy group substituted by at least one group as defined in claim 1, reacting a compound of formula (XIII):



(XIII)

wherein L^5 is a suitable displaceable group, W is an optionally substituted (C1-C6)alkyl, (C3-C6)alkenyl, (C3-C6)alkynyl or (C1-C6)alkoxy group and q, R^1, R^2, $-NQ^1$, Q^2

and Q^3 are as defined in claim 1 except that any functional group is protected if necessary, with a compound of formula H-Xa, (Xb), (Xc), (Xc') or M-R^3;

and optionally after process (a), (b), (c), (d), (e), (f), (g), (h), (i), (j) or (k) 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.