PYRIMIDINE DERIVATIVES AS MODULATORS OF INSULINE-LIKE GROWTH FACTOR-1 RECEPTOR (IGF-I)

The present invention relates to pyrimidine derivatives, a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

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 signaling 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 signaling 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 is a growing

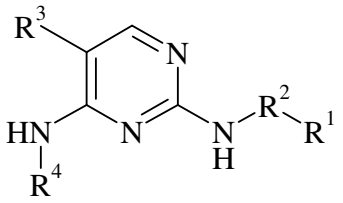
number of epidemiological studies linking increased circulating IGF (or increased ratio of IGF-1 to IGFBP3) with cancer risk (Yu and Rohan, *J. Natl.Cancer Inst.* , **92**, 1472-1489, 2000). Transgenic mouse models also implicate IGF signaling in the onset of tumour cell proliferation (Lamm and Christofori, *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 signaling 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 signaling is implicated in the growth and survival of tumour cells, and bloking 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 signaling, 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).

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



(I)

wherein

R^1 represents a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring being optionally substituted by at least one substituent selected from C_1-C_6alkyl, C_1-C_6alkoxy (each of which may be optionally substituted by at least one substituent selected from halogen, amino ($-NH_2$), hydroxyl and trifluoromethyl), halogen, nitro, cyano, $-NR^5R^6$, carboxyl, hydroxyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, C_1-C_6alkoxycarbonyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylcarbonylamino, phenylcarbonyl, $-S(O)_mC_1$-C_6alkyl, $-C(O)NR^7R^8$, $-SO_2NR^{7a}R^{8a}$, and an unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring itself being optionally substituted by at least one substituent selected from C_1-C_6alkyl, C_1-C_6alkoxy (each of which may be optionally substituted by at least one substituent selected from halogen, amino ($-NH_2$), hydroxyl and trifluoromethyl), halogen, nitro, cyano, $-NR^9R^{10}$, carboxyl, hydroxyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, C_1-C_6alkoxycarbonyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylcarbonylamino, phenylcarbonyl, $-S(O)_nC_1$-C_6alkyl, $-C(O)NR^{11}R^{12}$ and $-SO_2NR^{11a}R^{12a}$;

m is 0, 1 or 2;

n is 0, 1 or 2;

R^2 represents a C_1-C_4alkyl group optionally substituted by at least one substituent selected from halogen, hydroxyl and C_1-C_3alkoxy;

R^3 represents hydrogen, halogen or trifluoromethyl;

R^4 represents a 5-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring being optionally substituted by at least one substituent selected from C_1-C_6alkyl, C_1-C_6alkoxy (each of which may be optionally substituted by at least one substituent selected from halogen, amino ($-NH_2$), hydroxyl and trifluoromethyl), halogen, nitro, cyano, $-NR^{13}R^{14}$, carboxyl, hydroxyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, C_1-C_4alkoxycarbonyl, C_1-C_4alkylcarbonyl, C_1-C_4alkylcarbonylamino, phenylcarbonyl, $-S(O)_pC_1$-C_4alkyl, $-C(O)NR^{15}R^{16}$ and $-SO_2NR^{15a}R^{16a}$;

p is 0, 1 or 2;

R^5 and **R^6** each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^5 and R^6 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^7 and **R^8** each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^7 and R^8 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{7a} and **R^{8a}** each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{7a} and R^{8a} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^9 and **R^{10}** each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{11} and **R^{12}** each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{11a} and **R^{12a}** each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{11a} and R^{12a} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{13} and **R^{14}** each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{13} and R^{14} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{15} and **R^{16}** each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{15} and R^{16} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle; and

R^{15a} and **R^{16a}** each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{15a} and R^{16a} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

or a pharmaceutically acceptable salt or solvate thereof.

In the context of the present specification, unless otherwise indicated, an alkyl substituent group or an alkyl moiety in a substituent group may be linear or branched. When R^5 and R^6, or R^7 and R^8, or R^{7a} and R^{8a}, or R^9 and R^{10}, or R^{11} and R^{12}, or R^{11a} and R^{12a}, or R^{13} and R^{14}, or R^{15} and R^{16}, or R^{15a} and R^{16a} represent a saturated heterocycle, it should be

understood that the only heteroatom present is the nitrogen atom to which R^5 and R^6, or R^7 and R^8, or R^{7a} and R^{8a}, or R^9 and R^{10}, or R^{11} and R^{12}, or R^{11a} and R^{12a}, or R^{13} and R^{14}, or R^{15} and R^{16}, or R^{15a} and R^{16a} are attached. In the definition of R^1, it should be noted that the unsaturated 5- to 6-membered ring may have alicyclic or aromatic properties.

Examples of "C_1-C_6alkyl" and "C_1-C_4alkyl" include methyl, ethyl, isopropyl and *t*-butyl. Examples of "C_1-C_6alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C_1-C_6alkoxy" and "C_1-C_3alkoxy" include methoxy, ethoxy and propoxy. Examples of "C_1-C_6alkylcarbonylamino" include formamido, acetamido and propionylamino. Examples of "$S(O)_mC_1$-C_6alkyl" wherein m is 0 to 2 include methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C_1-C_6alkylcarbonyl" include propionyl and acetyl. Examples of "C_2-C_6alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C_3-C_6cycloalkyl" are cyclopropyl, cyclopentyl and cyclohexyl.

A "5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur" is a fully unsaturated, aromatic monocyclic ring containing 5 or 6 atoms of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur, which may, unless otherwise specified, be carbon or nitrogen linked. Suitably a "5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur" is pyridyl, imidazolyl, isoxazolyl, pyrazolyl, furyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl or thienyl; said pyridyl, imidazolyl, isoxazolyl, pyrazolyl, furyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl or thienyl.

An "unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur" is a fully or partially unsaturated, monocyclic ring containing 5 or 6 atoms optionally of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur, and which may, unless otherwise specified, be carbon or nitrogen linked. Suitably an "unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur" is phenyl or pyridyl.

A "5- membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur" is a fully unsaturated, aromatic monocyclic ring containing 5 atoms of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur, which may, unless otherwise specified, be carbon or nitrogen linked. Suitably a "5-

membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur" is pyrazolyl.

R^1 represents an optionally substituted 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur. Examples of heteroaromatic rings include thienyl (e.g. 3-thienyl), pyrazolyl (e.g. 4-pyrazolyl), isoxazolyl (e.g. 5-isoxazolyl), thiadiazolyl, pyrrolyl (e.g. 2-pyrrolyl), furanyl (2- or 3-furanyl), thiazolyl, triazolyl, tetrazolyl, imidazolyl (e.g. 4-imidazolyl), pyrazinyl (e.g. 2-pyrazinyl), pyridazinyl (e.g. 3-pyridazinyl), pyrimidinyl (e.g. 4- or 5-pyrimidinyl) and pyridyl (2-, 3- or 4-pyridyl).

In R^1, the 5- or 6-membered heteroaromatic ring is optionally substituted by at least one substituent (e.g. one, two, three or four substituents independently) selected from C_1-C_6, particularly C_1-C_4alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *tert*-butyl, n-pentyl or n-hexyl), C_1-C_6, particularly C_1-C_4alkoxy (such as methoxy, ethoxy, n-propoxy, n-butoxy, *tert*-butoxy, n-pentoxy or n-hexoxy) (each of the C_1-C_6alkyl and C_1-C_6alkoxy substituent groups being optionally substituted by at least one substituent, e.g. one, two, three or four substituents independently, selected from halogen (such as fluorine, chlorine bromine or iodine), amino, hydroxyl and trifluoromethyl), halogen (such as fluorine, chlorine, bromine or iodine), nitro, cyano, $-NR^5R^6$, carboxyl, hydroxyl, C_2-C_6, particularly C_2-C_4alkenyl (such as ethenyl), C_3-C_6cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), C_1-C_6, particularly C_1-C_4alkoxycarbonyl (such as methoxycarbonyl or ethoxycarbonyl), C_1-C_6, particularly C_1-C_4alkylcarbonyl (such as methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, n-pentylcarbonyl or n-hexylcarbonyl), C_1-C_6, particularly C_1-C_4alkylcarbonylamino (such as methylcarbonylamino or ethylcarbonylamino), phenylcarbonyl, $-S(O)_mC_1$-C_6, particularly C_1-C_4alkyl, $-C(O)NR^7R^8$, $-SO_2NR^{7a}R^{8a}$, and an optionally substituted unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur.

Examples of the unsaturated 5- to 6-membered ring include phenyl, cylopentenyl, cyclohexenyl, thienyl (e.g. 3-thienyl), pyrazolyl (e.g. 4-pyrazolyl), isoxazolyl (e.g. 5-isoxazolyl), thiadiazolyl, pyrrolyl (e.g. 2-pyrrolyl), furanyl (2- or 3-furanyl), thiazolyl, triazolyl, tetrazolyl, imidazolyl (e.g. 4-imidazolyl), pyrazinyl (e.g. 2-pyrazinyl), pyridazinyl (e.g. 3-pyridazinyl), pyrimidinyl (e.g. 4- or 5-pyrimidinyl) and pyridyl (2-, 3- or 4-pyridyl). The ring may itself be optionally substituted by at least one substituent (e.g. one, two, three or

four substituents independently) selected from C_1-C_6, particularly C_1-C_4alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *tert*-butyl, n-pentyl or n-hexyl), C_1-C_6, particularly C_1-C_4alkoxy (such as methoxy, ethoxy, n-propoxy, n-butoxy, *tert*-butoxy, n-pentoxy or n-hexoxy) (each of the C_1-C_6alkyl and C_1-C_6alkoxy substituent groups being optionally substituted by at least one substituent, e.g. one, two, three or four substituents independently, selected from halogen (such as fluorine, chlorine bromine or iodine), amino, hydroxyl and trifluoromethyl), halogen (such as fluorine, chlorine, bromine or iodine), nitro, cyano, $-NR^9R^{10}$, carboxyl, hydroxyl, C_2-C_6, particularly C_2-C_4alkenyl (such as ethenyl), C_3-C_6cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), C_1-C_6, particularly C_1-C_4alkoxycarbonyl (such as methoxycarbonyl or ethoxycarbonyl), C_1-C_6, particularly C_1-C_4alkylcarbonyl (such as methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, n-pentylcarbonyl or n-hexylcarbonyl), C_1-C_6, particularly C_1-C_4alkylcarbonylamino (such as methylcarbonylamino or ethylcarbonylamino), phenylcarbonyl, $-S(O)_nC_1$-C_6, particularly C_1-C_4alkyl, $-C(O)NR^{11}R^{12}$ and $-SO_2NR^{11a}R^{12a}$.

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

In one embodiment of the invention, R^1 represents a 5- or 6-membered heteroaromatic ring comprising one or two ring heteroatoms selected from nitrogen and oxygen, the ring being optionally substituted by at least one substituent selected from C_1-C_6alkyl, C_1-C_6alkoxy, halogen, nitro, cyano, $-NR^5R^6$, carboxyl, hydroxyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, C_1-C_6alkoxycarbonyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylcarbonylamino, phenylcarbonyl, $-S(O)_mC_1$-C_6alkyl, $-C(O)NR^7R^8$, $-SO_2NR^{7a}R^{8a}$, and an unsaturated 6-membered ring which may comprise one ring nitrogen atom, the ring itself being optionally substituted by at least one substituent selected from C_1-C_6alkyl, C_1-C_6alkoxy, halogen, nitro, cyano, $-NR^9R^{10}$, carboxyl, hydroxyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, C_1-C_6alkoxycarbonyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylcarbonylamino, phenylcarbonyl, $-S(O)_nC_1$-C_6alkyl, $-C(O)NR^{11}R^{12}$ and $-SO_2NR^{11a}R^{12a}$.

In a further embodiment of the invention, R^1 represents a 5- or 6-membered heteroaromatic ring comprising one or two ring heteroatoms selected from nitrogen and oxygen, the ring being optionally substituted by at least one substituent selected from C_1-C_6alkyl, C_1-C_6alkoxy, halogen, phenyl and pyridyl, each of the phenyl and pyridyl

substituent groups itself being optionally substituted by at least one substituent selected from C_1-C_6alkyl, C_1-C_6alkoxy and halogen.

In an additional aspect R^1 represents a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring being optionally substituted by at least one substituent selected from C_1-C_6alkyl, C_1-C_6alkoxy (each of which may be optionally substituted by at least one substituent selected from hydroxyl), halogen, -C(O)NR^7R^8, C_1-C_6alkoxycarbonyl, and an unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom selected from nitrogen and oxygen, the ring itself being optionally substituted by at least one substituent selected from C_1-C_6alkyl, C_1-C_6alkoxy (each of which may be optionally substituted by at least one substituent selected from halogen), halogen and cyano; wherein R^7 and R^8 are both hydrogen or R^7 and R^8 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle.

In a further additional aspect R^1 represents pyridyl, imidazolyl, isoxazolyl, pyrazolyl, furyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl or thienyl; said pyridyl, imidazolyl, isoxazolyl, pyrazolyl, furyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl and thienyl being optionally substituted by at least one substituent selected from methyl, isopropyl, hydroxymethyl, methoxy, chloro, bromo, carbamoyl, methoxycarbonyl, pyrrolidin-1-ylcarbonyl, phenyl and pyridyl; said phenyl or pyridyl being optionally substituted by at least one substituent selected from methyl, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, fluoro, chloro, bromo and cyano.

In a further additional aspect R^1 represents pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 2-methoxypyrid-5-yl, 2-cyanopyrid-5-yl, 3-bromopyrid-5-yl, 3-(pyrid-2-yl)pyrid-5-yl, 4-(pyrid-2-yl)pyrid-2-yl, 3-chloropyrid-2-yl, 3-methylpyrid-2-yl, 6-methylpyrid-2-yl, 5,6-dimethylpyrid-2-yl, imidazol-4-yl, imidazol-5-yl, 3-methylisoxazol-5-yl, 5-methylisoxazol-3-yl, 3-isopropylisoxazol-5-yl, 3-methoxycarbonylisoxazol-5-yl, 3-(hydroxymethyl)isoxazol-5-yl, 3-carbamoylisoxazol-5-yl, 3-(pyrrolidin-1-ylcarbonyl)isoxazol-5-yl, 3-phenylisoxazol-5-yl, 3-(pyrid-2-yl)isoxazol-5-yl, 3-(2-methoxypyrid-3-yl)isoxazol-5-yl, 3-(2-methoxyphenyl)isoxazol-5-yl, 3-(3-methoxyphenyl)isoxazol-5-yl, 3-(2-ethoxyphenyl)isoxazol-5-yl, 3-(2-trifluoromethylphenyl)isoxazol-5-yl, 3-(2-trifluoromethoxyphenyl)isoxazol-5-yl, 3-(2-chlorophenyl)isoxazol-5-yl, 3-(2-bromophenyl)isoxazol-5-yl, 3-(2-methylphenyl)isoxazol-5-yl, 3-(2-fluorophenyl)isoxazol-5-yl,

3-(2-cyanophenyl)isoxazol-5-yl, 5-methylpyrazol-4-yl, fur-2-yl, fur-3-yl, 5-methylfur-2-yl, pyrazin-2-yl, 2-methylpyrazin-5-yl, pyridazin-3-yl, pyrimidin-4-yl, 1-methylpyrrol-2-yl and thien-3-yl.

R^2 represents a C_1-C_4alkyl group (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or *tert*-butyl) optionally substituted by at least one substituent (e.g. one, two, three or four substituents independently) selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl and C_1-C_3alkoxy (e.g. methoxy, ethoxy and n-propoxy).

In one embodiment of the invention, R^2 represents CH_2 or $(CH_2)_2$.

In a further embodiment R^2 represents a C_1-C_4alkyl group.

In an additional embodiment R^2 represents methyl, ethyl and propyl.

R^3 represents hydrogen, halogen (e.g. fluorine, chlorine, bromine or iodine) or trifluoromethyl.

In one embodiment of the invention, R^3 represents chlorine or bromine.

In a further embodiment R^3 represents hydrogen or halogen.

In an additional embodiment R^3 represents hydrogen, chloro or bromo.

R^4 represents an optionally substituted 5-membered heteroaromatic ring comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur. Examples of rings include thienyl (e.g. 3-thienyl), pyrazolyl (e.g. 4-pyrazolyl), isoxazolyl (e.g. 5-isoxazolyl), thiadiazolyl, pyrrolyl (e.g. 2-pyrrolyl), furanyl (2- or 3-furanyl), thiazolyl, triazolyl, tetrazolyl, imidazolyl (e.g. 4-imidazolyl).

The 5-membered heteroaromatic ring in R^4 is optionally substituted by at least one substituent (e.g. one, two, three or four substituents independently) selected from C_1-C_6, particularly C_1-C_4alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *tert*-butyl, n-pentyl or n-hexyl), C_1-C_6, particularly C_1-C_4alkoxy (such as methoxy, ethoxy, n-propoxy, n-butoxy, *tert*-butoxy, n-pentoxy or n-hexoxy) (each of the C_1-C_6alkyl and C_1-C_6alkoxy substituent groups being optionally substituted by at least one substituent, e.g. one, two, three or four substituents independently, selected from halogen (such as fluorine, chlorine bromine or iodine), amino, hydroxyl and trifluoromethyl), halogen (such as fluorine, chlorine, bromine or iodine), nitro, cyano, $-NR^{13}R^{14}$, carboxyl, hydroxyl, C_2-C_6, particularly C_2-C_4alkenyl (such as ethenyl), C_3-C_6cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), C_1-C_4, particularly C_1-C_3alkoxycarbonyl (such as methoxycarbonyl or ethoxycarbonyl), C_1-C_4, particularly C_1-C_3alkylcarbonyl (such as methylcarbonyl,

ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl or n-butylcarbonyl), C_1-C_4, particularly C_1-C_3alkylcarbonylamino (such as methylcarbonylamino or ethylcarbonylamino), phenylcarbonyl, -$S(O)_pC_1$-C_4, particularly C_1-C_2alkyl, -$C(O)NR^{15}R^{16}$ and -$SO_2NR^{15a}R^{16a}$.

In one embodiment of the invention, R^4 represents a 5-membered heteroaromatic ring comprising one or two ring heteroatoms selected from nitrogen and oxygen, the ring being optionally substituted by at least one substituent selected from C_1-C_6alkyl, C_1-C_6alkoxy, halogen, nitro, cyano, -$NR^{13}R^{14}$, carboxyl, hydroxyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, C_1-C_4alkoxycarbonyl, C_1-C_4alkylcarbonyl, C_1-C_4alkylcarbonylamino, phenylcarbonyl, -$S(O)_pC_1$-C_4alkyl, -$C(O)NR^{15}R^{16}$ and -$SO_2NR^{15a}R^{16a}$.

In a further embodiment of the invention, R^4 represents a 5-membered heteroaromatic ring comprising two ring nitrogen atoms, the ring being optionally substituted by at least one substituent selected from C_1-C_6alkyl, C_1-C_6alkoxy, halogen and C_3-C_6cycloalkyl.

In an additional embodiment R^4 represents a 5-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, the ring being optionally substituted by at least one substituent selected from C_1-C_6alkyl and C_3-C_6cycloalkyl.

In an additional further embodiment R^4 represents pyrazolyl, the ring being optionally substituted by at least one substituent selected from methyl, ethyl, isopropyl, propyl, *t*-butyl and cyclopropyl.

In another further embodiment R^4 represents 5-methylpyrazol-3-yl, 5-ethylpyrazol-3-yl, 5-isopropylpyrazol-3-yl, 5-propylpyrazol-3-yl, 5-*t*-butylpyrazol-3-yl and 5-cyclopropylpyrazol-3-yl.

R^5 and R^6 each independently represent hydrogen, C_1-C_4, particularly C_1-C_2alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or *tert*-butyl) or C_3-C_6cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), or R^5 and R^6 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (such as pyrrolidinyl or piperidinyl).

R^7 and R^8 each independently represent hydrogen, C_1-C_4, particularly C_1-C_2alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or *tert*-butyl) or C_3-C_6cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), or R^7 and R^8 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (such as pyrrolidinyl or piperidinyl).

R^{7a} and R^{8a} each independently represent hydrogen, C_1-C_4, particularly C_1-C_2alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or *tert*-butyl) or C_3-C_6cycloalkyl

(cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), or R^{7a} and R^{8a} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (such as pyrrolidinyl or piperidinyl).

R^9 and R^{10} each independently represent hydrogen, C_1-C_4, particularly C_1-C_2alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or *tert*-butyl) or C_3-C_6cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (such as pyrrolidinyl or piperidinyl).

R^{11} and R^{12} each independently represent hydrogen, C_1-C_4, particularly C_1-C_2alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or *tert*-butyl) or C_3-C_6cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), or R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (such as pyrrolidinyl or piperidinyl).

R^{11a} and R^{12a} each independently represent hydrogen, C_1-C_4, particularly C_1-C_2alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or *tert*-butyl) or C_3-C_6cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), or R^{11a} and R^{12a} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (such as pyrrolidinyl or piperidinyl).

R^{13} and R^{14} each independently represent hydrogen, C_1-C_4, particularly C_1-C_2alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or *tert*-butyl) or C_3-C_6cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), or R^{13} and R^{14} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (such as pyrrolidinyl or piperidinyl).

R^{15} and R^{16} each independently represent hydrogen, C_1-C_4, particularly C_1-C_2alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or *tert*-butyl) or C_3-C_6cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), or R^{15} and R^{16} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (such as pyrrolidinyl or piperidinyl).

R^{15a} and R^{16a} each independently represent hydrogen, C_1-C_4, particularly C_1-C_2alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or *tert*-butyl) or C_3-C_6cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), or R^{15a} and R^{16a} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (such as pyrrolidinyl or piperidinyl).

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

R^1 represents a 5- or 6-membered heteroaromatic ring comprising one or two ring heteroatoms selected from nitrogen and oxygen, the ring being optionally substituted by at least one substituent selected from C_1-C_3alkyl, pyridyl, and phenyl optionally substituted by methoxy;

R^2 represents a C_1-C_2alkyl group;

R^3 represents chlorine or bromine; and

R^4 represents pyrazolyl substituted by at least one substituent selected from C_1-C_4alkyl and cyclopropyl.

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

R^1 represents a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring being optionally substituted by at least one substituent selected from C_1-C_6alkyl, C_1-C_6alkoxy (each of which may be optionally substituted by at least one substituent selected from hydroxyl), halogen, -C(O)NR^7R^8, C_1-C_6alkoxycarbonyl, and an unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom selected from nitrogen and oxygen, the ring itself being optionally substituted by at least one substituent selected from C_1-C_6alkyl, C_1-C_6alkoxy (each of which may be optionally substituted by at least one substituent selected from halogen), halogen and cyano; wherein R^7 and R^8 are both hydrogen or R^7 and R^8 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^2 represents a C_1-C_4alkyl group;

R^3 represents hydrogen or halogen; and

R^4 represents a 5-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, the ring being optionally substituted by at least one substituent selected from C_1-C_6alkyl and C_3-C_6cycloalkyl;

or a pharmaceutically acceptable salt or solvate thereof.

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

R^1 represents pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 2-methoxypyrid-5-yl, 2-cyanopyrid-5-yl, 3-bromopyrid-5-yl, 3-(pyrid-2-yl)pyrid-5-yl, 4-(pyrid-2-yl)pyrid-2-yl, 3-chloropyrid-2-yl, 3-methylpyrid-2-yl, 6-methylpyrid-2-yl, 5,6-dimethylpyrid-2-yl,

imidazol-4-yl, imidazol-5-yl, 3-methylisoxazol-5-yl, 5-methylisoxazol-3-yl, 3-isopropylisoxazol-5-yl, 3-methoxycarbonylisoxazol-5-yl, 3-(hydroxymethyl)isoxazol-5-yl, 3-carbamoylisoxazol-5-yl, 3-(pyrrolidin-1-ylcarbonyl)isoxazol-5-yl, 3-phenylisoxazol-5-yl, 3-(pyrid-2-yl)isoxazol-5-yl, 3-(2-methoxypyrid-3-yl)isoxazol-5-yl, 3-(2-methoxyphenyl)isoxazol-5-yl, 3-(3-methoxyphenyl)isoxazol-5-yl, 3-(2-ethoxyphenyl)isoxazol-5-yl, 3-(2-trifluoromethylphenyl)isoxazol-5-yl, 3-(2-trifluoromethoxyphenyl)isoxazol-5-yl, 3-(2-chlorophenyl)isoxazol-5-yl, 3-(2-bromophenyl)isoxazol-5-yl, 3-(2-methylphenyl)isoxazol-5-yl, 3-(2-fluorophenyl)isoxazol-5-yl, 3-(2-cyanophenyl)isoxazol-5-yl, 5-methylpyrazol-4-yl, fur-2-yl, fur-3-yl, 5-methylfur-2-yl, pyrazin-2-yl, 2-methylpyrazin-5-yl, pyridazin-3-yl, pyrimidin-4-yl, 1-methylpyrrol-2-yl and thien-3-yl;

R^2 represents methyl, ethyl and propyl;

R^3 represents hydrogen, chloro or bromo; and

R^4 represents 5-methylpyrazol-3-yl, 5-ethylpyrazol-3-yl, 5-isopropylpyrazol-3-yl, 5-propylpyrazol-3-yl, 5-*t*-butylpyrazol-3-yl and 5-cyclopropylpyrazol-3-yl;

or a pharmaceutically acceptable salt or solvate thereof.

Examples of compounds of the invention include:

5-Bromo-2-(3-methylisoxazol-5-ylmethylamino)-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Chloro-2-(3-methylisoxazol-5-ylmethylamino)-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Bromo-2-(3-methylisoxazol-5-ylmethylamino)-4-(5-cyclopropyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Chloro-2-(3-isopropylisoxazol-5-ylmethylamino)-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Chloro-2-(3-phenylisoxazol-5-ylmethylamino)-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Bromo-2-[3-(2-methoxyphenyl)isoxazol-5-ylmethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Chloro-2-[3-(2-methoxyphenyl)isoxazol-5-ylmethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Chloro-2-(3-pyrid-2-ylisoxazol-5-ylmethylamino)-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Bromo-2-(3-pyrid-2-ylisoxazol-5-ylmethylamino)-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Bromo-2-(3-methylisoxazol-5-ylmethylamino)-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Chloro-2-(3-methylisoxazol-5-ylmethylamino)-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Bromo-2-(3-methylisoxazol-5-ylmethylamino)-4-(5-ethyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Bromo-2-(2-fur-2-ylethylamino)-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Bromo-2-(pyrid-3-ylmethylamino)-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Chloro-2-(pyrid-3-ylmethylamino)-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Chloro-2-(pyrid-2-ylmethylamino)-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Bromo-2-(pyrid-3-ylmethylamino)-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Bromo-2-[2-(imidazol-4-ylethyl)amino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Bromo-2-(pyrid-2-ylmethylamino)-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Chloro-2-[2-(pyrid-2-yl)ethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Bromo-2-[2-(pyrid-3-yl)ethylamino]-4-(5-methyl-1*H*-pyrazol-3-yamino)pyrimidine,

5-Bromo-2-(5-methylpyrazin-2-ylmethylamino)-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Bromo-2-(pyrid-3-ylmethylamino)-4-(5-cyclopropyl-1*H*-pyrazol-3-ylamino)pyrimidine,

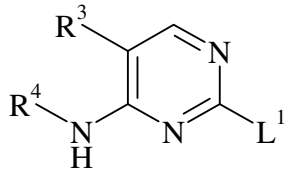
and pharmaceutically acceptable salts and solvates of any one thereof.

In a further aspect of the invention, particular compounds of the invention are any one of Examples 3, 5, 8, 9, 11, 12, 34, 39, 40, 41, 47, 48, 68, 70 and 79 or pharmaceutically acceptable salts and solvates of any one thereof.

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

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

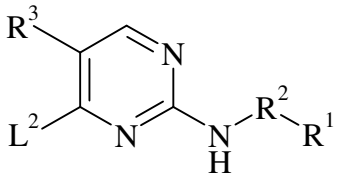
(i) reacting a compound of formula



(II)

wherein L^1 represents a leaving group (e.g. halogen or sulphonyloxy such as methanesulphonyloxy or toluene-4-sulphonyloxy) and R^3 and R^4 are as defined in formula **(I)**, with a compound of formula **(III)**, $H_2N\text{-}R^2\text{-}R^1$, wherein R^1 and R^2 are as defined in formula **(I)**; or

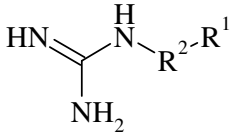
(ii) reacting a compound of formula



(IV)

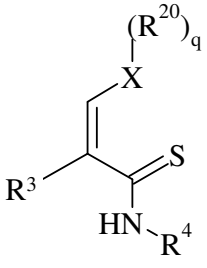
wherein L^2 represents a leaving group (e.g. halogen or sulphonyloxy such as methanesulphonyloxy or toluene-4-sulphonyloxy) and R^1, R^2 and R^3 are as defined in formula **(I)**, with a compound of formula **(V)**, $H_2N\text{-}R^4$, wherein R^4 is as defined in formula **(I)**; or

(iii) reacting a compound of formula



(VI)

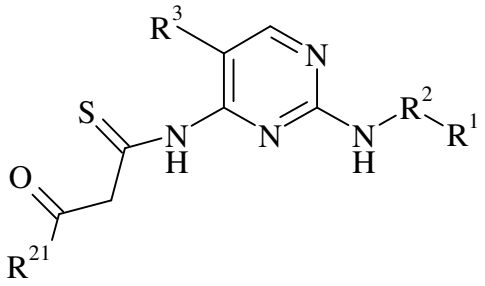
wherein R^1 and R^2 are as defined in formula **(I)**, with a compound of formula



(VII)

wherein X represents an oxygen atom and q is 1 or X represents a nitrogen atom and q is 2, each R^{20} independently represents a C_1-C_6alkyl group and R^3 and R^4 are as defined in formula **(I)**; or

(iv) when R^4 represents a substituted pyrazolyl, reacting a compound of formula



(VIII)

wherein R^{21} represents a C_1-C_6alkyl or C_3-C_6cycloalkyl group and R^1, R^2 and R^3 are as defined in formula **(I)** with hydrazine;

and optionally after (i), (ii), (iii) or (iv) carrying out one or more of the following:

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

Processes (i) and (ii) may conveniently be carried out as follows:

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

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

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

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

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

Compounds of formula **(I)** can be converted into further compounds of formula **(I)** using standard procedures. Examples of the types of conversion reactions that may be used include introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid; the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of reduction reactions include the reduction of a nitro group to an amino group by catalytic hydrogenation with a nickel catalyst or by treatment with iron in the presence of hydrochloric acid with heating; and particular examples of oxidation reactions include oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula **(I)** may involve, at various stages, the addition and removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

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

Certain compounds of formula **(I)** are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical

isomers (including atropisomers) of the compounds of formula **(I)** and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention. For example where R^4 is pyrazolyl; pyrazolyl-5-yl and pyrazolyl-3-yl are tautomers of the same compound.

The compounds of formula **(I)** have activity as pharmaceuticals, in particular as modulators or inhibitors of insulin-like growth factor-1 receptor (IGF-1R) activity, and may be used in the treatment of proliferative and hyperproliferative diseases/conditions, examples of which include the following cancers:

(1) carcinoma, including that of the bladder, brain, breast, colon, kidney, liver, lung, ovary, pancreas, prostate, stomach, cervix, thyroid and skin;

(2) hematopoietic tumors 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 and promyelocytic leukaemia;

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

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

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

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

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

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

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

The invention still further provides a method of modulating insulin-like growth factor-1 receptor (IGF-1R) activity which comprises administering to a patient in need thereof

a therapeutically effective amount of a compound of formula **(I)**, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

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

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

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

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

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

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as

ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

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

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

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

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting

agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

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

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

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

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

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

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

use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

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

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

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

In general, a compound of the invention will be administered so that a daily dose in the range, for example, from 0.5 mg to 75 mg active ingredient per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, from 0.5 mg to 30 mg active ingredient per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, from 0.5 mg to 25 mg active ingredient per kg body weight will generally be used. Oral administration is however preferred. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active ingredient.

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

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 18-25°C;

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

(iii) 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 +CD_3COOD unless otherwise indicated;

(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;
DMF	*N,N*-dimethylformamide;
EtOAc	ethyl acetate;
DCM	dichloromethane; and
DMSO	dimethylsulphoxide.

Example 1

5-Bromo-2-(3-methylisoxazol-5-ylmethylamino)-4-(5-methyl-1*H*-pyrazol-3-ylamino) pyrimidine

A mixture of 5-aminomethyl-3-methylisoxazole hydrochloride (890mg, 6.0mmol), 5-bromo-2-chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine (Method 1; 578mg,

2.0mmol) and *N*,*N*-diisopropylethylamine (1.4ml, 8.0mmol) in 1-butanol (10ml) was heated at 120ºC for 18 hours. The mixture was allowed to cool to ambient temperature and volatiles removed by evaporation. The residue was triturated with ether and the product collected by filtration to give the titled compound (225mg, 31%). ^{1}H NMR (DMSO): δ 2.15 (s, 3H), 2.2 (s, 3H), 4.5 (m, 2H), 6.1 (br s, 2H), 7.6 (br s, 1H), 8.0 (br s, 2H), 12.05 (br s, 1H); MS: m/z 366.

Examples 2 - 12

Following a similar procedure to Example 1, the following compounds were synthesised after replacement with a suitable pyrimidine (SM1) and amine (SM2) (the NMR was recorded in DMSO-d6). Where a starting material is not indicated, this compound is commercially available.

Ex	Compound	NMR	m/z	SM1	SM2
2 [1]	5-Chloro-2-(3-methylisoxazol-5-ylmethylamino)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidine	2.15 (s, 3H), 2.20 (s, 3H), 4.45 (d, 2H), 6.2-6.0 (m, 2H), 7.6 (br s, 1H), 7.95 (s, 1H), 8.5 (br s, 1H), 12.04 (br s, 1H)	320	Meth 10	
3 [1,2]	5-Bromo-2-(3-methylisoxazol-5-ylmethylamino)-4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrimidine	0.6 (br s, 2H), 0.9 (m, 2H), 1.8 (m, 1H), 2.15 (s, 3H), 4.5 (m, 2H), 6.0-6.2 (br s, 2H), 8.05 (s, 1H)	390	Meth 11	
4 [1]	5-Chloro-2-(3-isopropylisoxazol-5-ylmethylamino)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidine	1.2 (d, 6H), 2.2 (s, 3H), 2.9 (m, 1H), 4.5 (m, 2H), 6.2 (br s, 2H), 7.6 (br s, 1H), 7.98 (s, 1H), 12.04 (br s, 1H)	348	Meth 10	Meth 57
5 [1,2]	5-Chloro-2-(3-phenylisoxazol-5-ylmethylamino)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidine	2.2 (s, 3H), 4.6 (m, 2H), 6.78 (s, 1H), 7.4 (m, 3H), 7.6 (br s, 1H), 7.8 (m, 2H), 8.0 (s, 1H), 8.45 (s, 1H), 12.0 (br s, 1H)	382	Meth 10	Meth 56
6	5-Bromo-2-[3-(2-	2.2 (s, 3H), 3.8 (s, 3H), 4.6	456	Meth	Meth

[1,2]	methoxyphenyl)isoxazol-5-ylmethylamino]-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidine	(m, 2H), 6.0-6.2 (m, 1H), 6.6 (s, 1H), 7.0 (t, 1H), 7.1 (d, 1H), 7.45 (m, 1H), 7.7 (s, 2H), 8.1 (s, 2H), 12.1 (br s, 1H)		1	58
7 [1,2]	5-Chloro-2-[3-(2-methoxyphenyl)isoxazol-5-ylmethylamino]-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidine	2.2 (s, 3H), 3.8 (s, 3H), 4.5-4.7 (m, 2H), 6.0-6.4 (br s, 1H), 6.6 (s, 1H), 7.0 (t, 1H), 7.15 (d, 1H), 7.45 (m, 1H), 7.55-7.7 (m, 2H), 8.0 (s, 1H), 8.5 (br s, 1H), 12.05 (s, 1H)	412	Meth 10	Meth 58
8	5-Chloro-2-(3-pyrid-2-ylisoxazol-5-ylmethylamino)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidine	2.2 (s, 3H), 4.6 (m, 2H), 6.7 (s, 1H), 7.43 (m, 1H), 7.63 (br s, 1H), 7.9-8.0 (m, 3H), 8.48 (s, 1H), 8.65 (d, 1H), 12.02 (br s, 1H)	383	Meth 10	Meth 70
9 [1]	5-Bromo-2-(3-pyrid-2-ylisoxazol-5-ylmethylamino)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidine	2.2 (s, 3H), 4.6 (m, 2H), 6.0-6.6 (m, 1H), 6.7 (s, 1H), 7.5 (m, 1H), 7.7 (br s, 1H), 7.9-8.2 (m, 4H), 8.7 (d, 1H), 12.1 (br s, 1H)	427	Meth 1	Meth 70
10 [1,2]	5-Bromo-2-(3-methylisoxazol-5-ylmethylamino)-4-(5-*tert*-butyl-1H-pyrazol-3-ylamino)pyrimidine	1.25 (s, 9H), 2.05 (s, 3H), 4.50 (d, 2H), 6.05 (s, 1H), 7.60 (s, 1H), 8.05 (s, 1H), 12.07 (s, 1H)	406	Meth 12	
11 [1,2]	5-Chloro-2-(3-methylisoxazol-5-ylmethylamino)-4-(5-*tert*-butyl-1H-pyrazol-3-ylamino)pyrimidine	1.23 (s, 9H), 2.13 (s, 3H), 4.50 (d, 2H), 6.03 (br s, 1H), 6.32 (br s, 1H,), 7.55 (br s, 1H), 7.95 (s, 1H), 12.05 (br s, 1H)	362	Meth 13	
12 [2]	5-Bromo-2-(3-methylisoxazol-5-	1.16 (t, 3H), 2.13 (s, 3H), 2.53 (q, 2H), 4.47 (d, 2H),	378	Meth 14	

	ylmethylamino)-4-(5-ethyl-1H-pyrazol-3-ylamino)pyrimidine	6.05 (s, 1H), 7.58 (s, 1H), 8.03 (br s, 2H), 12.06 (s, 1H)			

[1] Required aqueous work-up.

[2] Purified by column chromatography on silica gel eluting with DCM/methanol (95:5).

Example 13

5-Bromo-2-(2-fur-2-ylethylamino)-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine

A mixture of 5-bromo-2-chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine (Method 1; 290mg, 1.0mmol), 2-(2-aminoethyl)furan (330mg, 3.0mmol) and 1-butanol (5ml) was heated at 120ºC for 5 hours. The mixture was allowed to cool to ambient temperature and the volatiles removed by evaporation. The residue was dissolved in DCM and washed with water followed by brine. The organics were separated, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was triturated with ether, the solid product collected and purified by column chromatography on silica gel eluting with DCM /methanol (95:5) to give the titled compound (80mg, 22%). ^{1}H NMR (DMSO): δ 2.1 (s, 3H), 2.85 (m, 2H), 3.45 (m 2H), 6.10 (m, 1H), 6.35 (m, 1H), 6.4 (br s, 1H), 7.15 (br s, 1H), 7.5 (s, 1H), 8.0 (br s, 2H), 12.05 (br s, 1H); MS: m/z 363 .

Examples 14 - 106

Following a similar procedure to Example 13, the following compounds were synthesised after replacement with appropriate pyrimidine (SM1) and amine (SM2) starting materials. Where a starting material is not indicated, this compound is commercially available.

Ex	Compound	NMR	m/z	SM1	SM2
14 [1,7]	5-Bromo-2-(pyrid-3-ylmethylamino)-4-(5-*tert*-butyl-1H-pyrazol-3-ylamino)pyrimidine	1.20 (s, 9H), 4.50 (d, 2H), 6.05 (s, 1H), 7.30 (m, 1H), 7.60 (m, 3H), 8.00 (s, 2H), 8.40 (d, 1H), 8.45 (s, 1H), 12.07 (s, 1H)	402	Meth 12	
15 [2,7]	5-Chloro-2-(pyrid-3-ylmethylamino)-4-(5-*tert*-butyl-1H-pyrazol-3-ylamino)pyrimidine	1.19 (s, 9H), 4.47 (d, 2H), 7.28 (t, 1H)	358	Meth 13	

16 [2,7]	5-Chloro-2-(pyrid-2-ylmethylamino)-4-(5-*tert*-butyl-1H-pyrazol-3-ylamino)pyrimidine	1.14 (s, 9H), 4.56 (d, 2H), 6.17 (br s, 1H), 7.61 (s, 1H), 7.69 (t, 1H), 7.94 (s, 1H), 8.39 (s, 1H), 8.46 (d, 1H), 12.01 (s, 1H)	358	Meth 13	
17 [3,7]	5-Bromo-2-(pyrid-3-ylmethylamino)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidine	2.17 (s, 3H), 4.42 (d, 2H), 7.28 (m, 1H), 7.6 (m, 2H), 8.0 (br s, 2H), 8.4 (d, 1H), 8.5 (s, 1H), 12.01 (br s, 1H)	360	Meth 1	
18 [3,7]	5-Bromo-2-[2-(imidazol-4-ylethyl)amino]-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidine	2.2 (s, 3H), 2.75 (t, 2H), 3.45 (m, 2H), 6.4 (br s, 1H), 6.85 (s, 1H), 7.15 (br s, 1H), 7.5 (s, 1H), 8.0 (br s, 1H)	363	Meth 1	
19 [4,5,7]	5-Bromo-2-(pyrid-2-ylmethylamino)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidine	2.1 (br s, 3H), 4.5 (d, 2H), 7.2 (m, 2H), 7.6 (br s, 1H), 7.7 (m, 1H), 7.9 (s, 1H), 8.0 (s, 1H), 8.5 (d, 1H), 11.97 (br s, 1H)	360	Meth 1	
20 [7]	5-Chloro-2-[2-(pyrid-2-yl)ethylamino]-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidine	2.15 (s, 3H), 2.95 (m, 2H), 3.6 (m, 2H), 6.5 (s, 1H), 7.05 (br s, 1H), 7.2 (m, 2H), 7.65 (t, 1H), 7.9 (s, 1H), 8.3 (br s, 1H), 8.5 (m, 1H), 12.02 (br s, 1H)	330	Meth 10	
21 [4,5,7]	5-Bromo-2-[2-(pyrid-3-yl)ethylamino]-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidine	2.1 (br s, 3H), 2.9 (t, 2H), 3.5 (t, 2H), 6.4 (s, 1H), 6.95 (t, 1H), 7.05 (t, 1H), 7.1 (s, 1H), 7.3 (d, 1H), 7.5 (m, 1H), 8.0 (s, 1H)	374	Meth 1	
22 [4,5,6,7]	5-Bromo-2-(5-methylpyrazin-2-ylmethylamino)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidine	2.2 (s, 3H), 2.45 (s, 3H), 4.6 (d, 2H), 6.2 (s, 1H), 7.15 (br s, 1H), 8.0 (s, 1H), 8.4 (s, 1H), 8.43 (s, 1H)	375	Meth 1	
23 [7]	5-Bromo-2-(pyrid-3-ylmethylamino)-4-(5-	0.4-0.9 (m, 4H), 1.8 (br s, 1H), 4.4 (m, 2H), 5.8-6.5 (m, 1H), 7.3 (m,	386	Meth 11	

	cyclopropyl-1H-pyrazol-3-ylamino)pyrimidine	1H), 7.6 (br s, 2H), 8.0 (s, 2H), 8.4 (m, 1H), 8.5 (s, 1H), 12.1-12.3 (m, 1H)			
24	5-Bromo-2-[3-(2-chlorophenyl)isoxazol-5-ylmethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	2.19 (s, 3H), 4.64 (s, 2H), 5.74 (s, 1H), 6.18 (br s, 1H), 6.64 (s, 1H), 7.41-7.55 (m, 2H), 7.74 (t, 1H), 8.07 (s, 1H)	460	Meth 1	Meth 59
25	5-Bromo-2-[3-(2-chlorophenyl)isoxazol-5-ylmethylamino]-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.21 (s, 9H), 4.67 (s, 2H), 6.31 (br s, 1H), 6.60 (br s, 1H), 7.39-7.54 (m, 2H), 7.56-7.66 (m, 2H), 8.07 (s, 1H)	502	Meth 12	Meth 59
26	4-(5-Methyl-1*H*-pyrazol-3-ylamino)-2-(pyrid-3-ylmethylamino) pyrimidine	2.12 (s, 3H), 4.46 (s, 2H), 6.05 (br s, 1H), 6.21 (br s, 1H), 7.26-7.35 (m, 2H), 7.70 (d, 1H), 7.79 (d, 1H), 8.39 (s, 1H), 8.55 (s, 1H)	282	Meth 15	
27	5-Bromo-2-[2-(3-methylisoxazol-5-yl)ethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	2.18 (s, 6H), 2.96 (t, 2H), 3.51 (t, 2H), 6.12 (s, 1H), 6.36 (s, 1H), 8.02 (s, 1H)	378	Meth 1	Meth 83
28	5-Chloro-2-[3-(2-chlorophenyl)isoxazol-5-ylmethylamino]-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.21 (s, 9H), 4.65 (s, 2H), 6.31 (br s, 1H), 6.60 (br s, 1H), 7.39-7.52 (m, 2H), 7.57-7.65 (m, 2H), 7.99 (s, 1H)	458	Meth 13	Meth 59
29	5-Chloro-4-(5-propyl-1*H*-pyrazol-3-ylamino)-2-(pyrid-2-ylmethylamino) pyrimidine	0.88 (t, 3H), 1.50 (br s, 2H), 2.44 (br s, 2H), 4.53 (s, 2H), 5.87 (br s, 1H), 7.16-7.29 (m, 2H), 7.70 (t, H), 7.94 (s, 1H), 8.48 (d, 1H)	344	Meth 16	
30	5-Bromo-4-(5-	0.60 (br s, 2H), 0.89 (d, 2H), 1.78	386	Meth	

	cyclopropyl-1*H*-pyrazol-3-ylamino)-2-(pyrid-2-ylmethylamino) pyrimidine	(br s, 1H), 4.51 (s, 2H), 5.87 (br s, 1H), 7.16-7.31 (m, 2H), 7.69 (t, 1H), 8.01 (s, 1H), 8.49 (d, 1H)		11	
31	5-Chloro-4-(5-ethyl-1*H*-pyrazol-3-ylamino)-2-(pyrid-2-ylmethylamino) pyrimidine	1.10 (br s, 3H), 2.44 (br s, 2H), 4.49 (s, 2H), 6.01 (br s, 1H), 7.17-7.29 (m, 2H), 7.70 (t, 1H), 7.93 (s, 1H), 8.49 (d, 1H)	330	Meth 17	
32	5-Bromo-4-(5-ethyl-1*H*-pyrazol-3-ylamino)-2-(pyrid-2-ylmethylamino) pyrimidine	1.10 (br s, 3H), 2.54 (br s, 2H), 4.54 (s, 2H), 6.00 (br s, 1H), 7.17-7.30 (m, 2H), 7.69 (t, 1H), 7.99 (s, 1H), 8.49 (d, 1H)	374	Meth 14	
33 [7]	5-Bromo-4-(5-propyl-1*H*-pyrazol-3-ylamino)-2-(pyrid-2-ylmethylamino) pyrimidine	0.88 (br s, 3H), 1.51 (br s, 2H), 2.45 (br s, 2H), 4.55 (s, 2H), 5.98 (br s, 1H), 7.15-7.30 (m, 2H), 7.59 (s, 1H), 7.72 (t, 1H), 7.95 (s, 1H), 8.01 (s, 1H), 8.50 (d, 1H), 11.98 (s, 1H)	388	Meth 18	
34 [7]	5-Chloro-2-[3-(2-fluorophenyl)isoxazol-5-ylmethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	2.19 (s, 3H), 4.61 (s, 2H), 6.21 (br s, 1H), 6.66 (s, 1H), 7.27-7.40 (m, 2H), 7.50-7.60 (m, 1H), 7.66 (br s, 1H), 7.86 (t, 1H), 7.99 (s, 1H), 8.50 (br s, 1H), 12.04 (s, 1H)	400	Meth 10	Meth 60
35	5-Chloro-4-(5-isopropyl-1*H*-pyrazol-3-ylamino)-2-(pyrid-2-ylmethylamino) pyrimidine	1.15 (br s, 6H), 2.81 (br s, 1H), 4.55 (s, 2H), 6.20 (br s, 1H), 7.15-7.32 (m, 2H), 7.71 (t, 1H), 7.95 (s, 1H), 8.46 (d, 1H)	344	Meth 19	
36 [7]	5-Bromo-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)-2-[3-(2-trifluoromethoxyphenyl) isoxazol-5-	1.26 (s, 9H), 4.65 (s, 2H), 6.28 (br s, 1H), 6.56 (br s, 1H), 7.46-7.56 (m, 2H), 7.62-7.66 (m, 1H), 7.72 (br s, 1H), 7.85 (d, 1H), 8.05 (s, 1H), 12.06 (s, 1H)	552	Meth 12	Meth 61

	ylmethylamino] pyrimidine				
37	5-Chloro-4-(5-cyclopropyl-1*H*-pyrazol-3-ylamino)-2-(pyrid-2-ylmethylamino) pyrimidine	0.60 (br s, 2H), 0.88 (d, 2H), 1.78 (br s, 1H), 4.52 (s, 2H), 5.95 (br s, 1H), 7.16-7.31 (m, 2H), 7.69 (t, 1H), 7.91 (s, 1H), 8.50 (d, 1H)	342	Meth 20	
38 [8]	5-Chloro-2-[3-(2-cyanophenyl)isoxazol-5-ylmethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	2.18 (s, 3H), 4.68 (s, 2H), 6.27 (s, 1H), 6.77 (s, 1H), 7.64 (dt, 1H), 7.77 (dt, 1H), 7.84 (dd, 1H), 7.90 (dd, 1H), 7.96 (s, 1H)	407	Meth 10	Meth 81
39	5-Bromo-2-[3-(2-fluorophenyl)isoxazol-5-ylmethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	2.19 (s, 3H), 4.63 (s, 2H), 6.27 (br s, 1H), 6.66 (s, 1H), 7.30-7.44 (m, 2H), 7.50-7.61 (m, 1H), 7.87 (t, 1H), 8.09 (s, 1H)	444	Meth 1	Meth 60
40 [7]	5-Chloro-2-[3-(2-fluorophenyl)isoxazol-5-ylmethylamino]-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.22 (s, 9H), 4.67 (s, 2H), 6.38 (br s, 1H), 6.64 (br s, 1H), 7.28-7.41 (m, 2H), 7.50-7.59 (m, 1H), 7.69 (br s, 1H), 7.85 (t, 1H), 8.00 (s, 1H), 8.54 (br s, 1H), 12.10 (s, 1H)	442	Meth 13	Meth 60
41	5-Bromo-4-(5-isopropyl-1*H*-pyrazol-3-ylamino)-2-(pyrid-2-ylmethylamino) pyrimidine	1.01-1.25 (m, 6H), 2.84 (br s, 1H), 4.56 (s, 2H), 6.12 (br s, 1H), 7.19-7.34 (m, 2H), 7.72 (t, 1H), 8.04 (s, 1H), 8.49 (d, 1H)	388	Meth 21	
42 [7]	5-Bromo-2-[3-(2-fluorophenyl)isoxazol-5-ylmethylamino]-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.22 (s, 9H), 4.66 (s, 2H), 6.34 (br s, 1H), 6.62 (br s, 1H), 7.28-7.43 (m, 2H), 7.51-7.61 (m, 1H), 7.72 (br s, 1H), 7.86 (t, 1H), 8.01-8.18 (br s, 2H), 12.10 (s, 1H)	486	Meth 12	Meth 60
43 [8]	5-Bromo-2-[3-(2-	1.69 (s, 3H), 4.20 (s, 2H), 5.78 (s,	451	Meth	Meth

	cyanophenyl)isoxazol-5-ylmethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	1H), 6.27 (s, 1H), 7.15 (dt, 1H), 7.28 (dt, 1H), 7.35 (dd, 1H) 7.41 (dd, 1H), 7.55 (s, 1H)		1	81
44 [9]	5-Bromo-2-[1-(3-methylisoxazol-5-yl)ethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.50 (s, 3H), 2.18 (s, 3H), 2.22 (s, 3H), 5.18 (q, H), 6.10 (s, H), 6.23 (br s, H), 7.68 (br s, H), 8.09 (s, H), 8.53 (br s, H)	378	Meth 1	Meth 72
45 [9]	5-Chloro-2-[1-(3-methylisoxazol-5-yl)ethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.50 (s, 3H), 2.15 (s, 3H), 2.24 (s, 3H), 5.18 (q, H), 6.10 (s, H), 6.21 (br s, H), 7.73 (br s, H), 8.01 (s, H), 8.99 (br s, H)	334	Meth 10	Meth 72
46 [7]	5-Bromo-4-(5-ethyl-1*H*-pyrazol-3-ylamino)-2-(pyrid-3-ylmethylamino) pyrimidine	1.10 (t, 3H), 2.54 (q, 2H), 4.42 (d, 2H), 7.26 (t, 1H), 7.50-7.68 (m, 2H), 7.92-8.05 (m, 2H), 8.37 (d, 1H), 8.45 (s, 1H), 12.04 (br s, 1H)	374	Meth 14	
47	5-Bromo-2-(3-methylisoxazol-5-ylmethylamino)-4-(5-propyl-1*H*-pyrazol-3-ylamino)pyrimidine	0.85 (t, 3H), 1.58 (m, 2H), 2.10 (s, 3H), 2.50 (t, 2H), 4.50 (s, 2H), 6.05 (s, 1H), 8.00 (s, 1H)	392	Meth 18	
48	5-Bromo-2-(3-methylisoxazol-5-ylmethylamino)-4-(5-isopropyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.18 (d, 6H), 2.10 (s, 3H), 2.85 (m, 1H), 4.5 (s, 2H), 6.00 (s, 1H), 6.30 (br s, 1H), 8.00 (s, 1H)	392	Meth 21	
49	5-Bromo-2-[3-(2-ethoxyphenyl)isoxazol-5-ylmethylamino]-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.25 (br s, 12H), 4.04 (q, 2H), 4.62 (s, 2H), 6.35 (br s, 1H), 6.65 (s, 1H), 7.00 (t, 1H), 7.10 (d, 1H), 7.40 (t, 1H), 7.70 (d, 1H), 8.07 (s, 1H)	512	Meth 12	Meth 62

50	5-Bromo-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)-2-[3-(2-trifluoromethylphenyl) isoxazol-5-ylmethylamino] pyrimidine	1.30 (s, 9H), 4.75 (s, 2H), 6.35 (br s, 1H), 6.43 (br s, 1H), 7.58 (d, 1H), 7.75 (m, 2H), 7.87 (d, 1H), 8.20 (s, 1H)	536	Meth 12	Meth 63
51	5-Bromo-2-[3-(2-methylphenyl)isoxazol-5-ylmethylamino]-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.23 (s, 9H), 2.36 (s, 3H), 4.65 (s, 2H), 6.36 (br s, 1H), 6.54 (br s, 1H), 7.32 (m, 3H), 7.44 (d, 1H), 8.20 (s, 1H)	482	Meth 12	Meth 64
52 [7]	5-Bromo-2-[2-(pyridazin-3-yl)ethylamino]-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.19 (br s, 9H), 3.19 (t, 2H), 3.65 (q, 2H), 6.41 (br s, 1H), 7.54 (m, 2H), 7.98 (s, 1H), 9.06 (d, 1H)	417	Meth 12	J Am Chem Soc, 1950, 72, 3539
53	5-Bromo-2-[3-(2-bromophenyl)isoxazol-5-ylmethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	2.18 (s, 3H), 4.63 (s, 2H), 6.3 (bd, 1H), 6.62 (br s, 1H), 7.49 (m, 3H), 7.76 (d, 1H), 8.07 (s, 1H)	506	Meth 1	Meth 65
54	5-Bromo-2-[2-(pyrimidin-4-yl)ethylamino]-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.19 (s, 9H), 2.98 (t, 2H), 3.62 (q, 2H), 6.36 (s, 1H), 7.37 (d, 1H), 8.13 (s, 1H), 8.62 (d, 1H), 9.04 (s, 1H)	417	Meth 12	J Am Chem Soc, 1950, 72, 3539
55 [7]	5-Bromo-2-(pyrazin-2-ylmethylamino)-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.19 (s, 9H), 4.57 (d, 2H), 6.16 (br s, 1H), 8.01 (s, 1H), 8.48 (s, 1H), 8.52 (s, 2H)	403	Meth 12	

56	5-Bromo-2-(5-methylisoxazol-3-ylmethylamino)-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.24 (s, 9H), 2.38 (s, 3H), 4.43 (s, 2H), 6.07 (s, 1H), 6.41 (s, 1H), 8.04 (s, 1H)	406	Meth 12	Meth 85
57 [7]	5-Bromo-2-(pyrid-3-ylmethylamino)-4-(5-propyl-1*H*-pyrazol-3-ylamino)pyrimidine	0.86 (t, 3H), 1.52 (m, 2H), 2.47 (m, 2H), 4.45 (d, 2H), 6.04 (br s, 1H), 7.29 (t, 1H), 7.60 (bt, 1H), 8.00 (s, 1H), 8.39 (d, 1H), 8.48 (s, 1H)	388	Meth 18	
58	5-Bromo-4-(5-isopropyl-1H-pyrazol-3-ylamino)-2-(pyrid-3-ylmethylamino) pyrimidine	1.14 (s, 6H), 2.84 (m, 1H), 4.46 (s, 2H), 6.18 (br s, 1H), 7.28 (t, 1H), 7.63 (bt, 1H), 8.00 (s, 1H), 8.38 (d, 1H), 8.47 (s, 1H)	388	Meth 21	
59	5-Bromo-2-[3-(2-methoxypyrid-3-yl)isoxazol-5-ylmethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	2.19 (s, 3H), 3.93 (s, 3H), 4.62 (s, 2H), 6.30 (br s, 1H), 6.70 (s, 1H), 7.12 (dd, 1H), 8.07 (s, 1H), 8.14 (dd, 1H), 8.29 (dd, 1H)	457	Meth 1	Meth 66
60 [7]	5-Bromo-2-[3-(3-methylpyrazol-4-yl)propylamino]-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.25 (s, 9H), 1.71 (m, 2H), 2.06 (s, 3H), 2.34 (m, 2H), 3.24 (m, 2H), 6.47 (br s, 1H), 7.05 (br s, 1H), 7.30 (br s, 1H), 7.97 (s, 1H), 12.06 (br s, 1H)	433	Meth 12	
61 [7]	5-Bromo-2-[3-(3-methylpyrazol-4-yl)propylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.70 (m, 2H), 2.08 (s, 3H), 2.18 (s, 3H), 2.36 (t, 2H), 3.20 (m, 2H), 6.40 (br s, 1H), 7.03 (br s, 1H), 7.26 (s, 1H), 7.97 (s, 2H), 12.04 (s, 1H)	391	Meth 1	
62	5-Chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)-	2.12 (s, 3H), 4.5 (d, 2H), 7.07-7.36 (m, 2H), 7.51 (br s, 1H), 7.67	316	Meth 10	

	2-(pyrid-2-ylmethylamino) pyrimidine	(m, 1H), 7.91 (s, 1H), 8.34 (s, 1H), 8.48 (d, 1H), 11.96 (br s, 1H)			
63	5-Chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2-(pyrid-3-ylmethylamino) pyrimidine	2.15 (s, 3H), 4.43 (m, 2H), 7.29 (s, 1H), 7.43-7.74 (m, 2H), 7.92 (br s, 1H), 8.23-8.56 (m, 3H), 12.0 (br s, 1H)	316	Meth 10	
64	5-Bromo-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2-(pyrid-4-ylmethylamino) pyrimidine	2.13 (s, 3H), 4.43 (d, 2H), 7.24 (d, 2H), 7.63 (br s, 1H), 7.99 (s, 2H), 8.44 (d, 2H), 11.99 (br s, 1H)	360	Meth 1	
65	5-Chloro-2-[2-(imidazol-5-yl)ethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	2.15 (s, 3H), 2.74 (m, 2H), 3.43 (m, 2H), 6.48 (br s, 1H), 6.77 (br s, 1H), 7.01 (br s, 1H), 7.5 (s, 1H), 7.9 (br s, 1H), 8.31 (br s, 1H), 11.6-12.1 (m, 2H)	319	Meth 10	
66	5-Chloro-2-[3-(3-methoxyphenyl)isoxazol-5-ylmethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	2.19 (s, 3H), 3.81 (s, 3H), 4.61 (s, 2H), 6.05-6.45 (m, 1H), 6.81 (s, 1H), 7.03 (m, 1H), 7.36-7.40 (m, 4H), 7.99 (s, 1H)	412	Meth 10	Meth 67
67	5-Chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2-[3-(pyrid-3-yl)isoxazol-5-ylmethylamino] pyrimidine	2.16 (s, 3H), 4.60 (s, 2H), 5.97-6.43 (m, 1H), 6.88 (br s, 1H), 7.49 (m, 1H), 7.96 (s, 1H), 8.20 (m, 1H), 8.64 (m, 1H), 9.0 (br s, 1H)	383	Meth 10	Meth 68
68	5-Chloro-2-[3-(pyrid-2-yl)isoxazol-5-ylmethylamino]-4-(5-*tert*-butyl-1*H*-pyrazol-3-	1.24 (s, 9H), 4.66 (s, 2H), 6.34 (br s, 1H), 6.73 (br s, 1H), 7.48 (t, 1H), 7.89-7.99 (m, 3H), 8.65 (d, 1H)	425	Meth 13	Meth 70

	ylamino)pyrimidine				
69	5-Bromo-4-(5-propyl-1*H*-pyrazol-3-ylamino)-2-[3-(pyrid-2-yl)isoxazol-5-ylmethylamino] pyrimidine	0.85 (br s, 3H), 1.55 (br s, 2H), 2.5 (2H, m), 4.63 (s, 2H), 6.05-6.52 (m, 1H), 6.74 (br s, 1H), 7.47 (t, 1H), 7.88-7.99 (m, 2H), 8.07 (s, 1H), 8.66 (d, 1H)	455	Meth 18	Meth 70
70	5-Bromo-2-[3-(pyrid-2-yl)isoxazol-5-ylmethylamino]-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.23 (s, 9H), 4.66 (s, 2H), 6.34 (br s, 1H), 6.73 (br s, 1H), 7.48 (m , 1H), 7.86-8.02 (m, 2H), 8.08 (s, 1H), 8.65 (d, 1H)	469	Meth 12	Meth 70
71	5-Bromo-4-(5-ethyl-1*H*-pyrazol-3-ylamino)-2-[3-(pyrid-2-yl)isoxazol-5-ylmethylamino] pyrimidine	1.15 (m, 3H), 2.54 (m, 2H), 4.64 (s, 2H), 6.05-6.53 (br s, 1H), 6.74 (br s, 1H), 7.46 (m, 1H), 7.84-8.02 (m, 2H), 8.07 (s, 1H), 8.65 (d, 1H)	441	Meth 14	Meth 70
72	5-Bromo-4-(5-isopropyl-1*H*-pyrazol-3-ylamino)-2-[3-(pyrid-2-yl)isoxazol-5-ylmethylamino] pyrimidine	1.17 (m, 6H), 2.80-2.95 (m, 1H), 4.64 (br s, 1H), 6.18-6.48 (br s, 1H), 6.73 (br s, 1H), 7.46 (m, 1H), 7.82-8.00 (m, 2H), 8.07 (s, 1H), 8.64 (d, 1H)	455	Meth 21	Meth 70
73 [10]	5-Bromo-2-(5-methylfur-2-ylmethylamino)-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.24 (s, 9H), 2.21 (s, 3H), 4.48 (s, 2H), 5.97 (s, 1H), 6.06 (br s, 1H), 6.40 (br s, 1H), 8.32 (s, 1H)	405	Meth 12	
74 [10]	5-Bromo-2-(fur-3-ylmethylamino)-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	2.25 (s, 3H), 4.37 (s, 2H), 6.24 (s, 1H), 6.47 (s, 1H), 7.52 (s, 1H), 7.61 (s, 1H), 8.35 (s, 1H)	349	Meth 1	
75 [10]	5-Bromo-2-(2-cyanopyrid-5-	1.15 (s, 9H), 4.62 (s, 2H), 6.05 (s, 1H), 7.86 (m, 1H), 7.93 (d, 1H),	427	Meth 12	WO 02 /

	ylmethylamino)-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine	8.38 (s, 1H), 8.60 (s, 1H)			44145
76 [10]	5-Bromo-2-(pyrid-2-ylmethylamino)-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.19 (s, 9H), 4.87 (s, 2H), 6.04 (s, 1H), 7.90 (m, 2H), 8.46 (m, 2H), 8.83 (d, 1H)	402	Meth 12	
77 [10]	5-Bromo-2-(fur-3-ylmethylamino)-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.24 (s, 9H), 4.40 (s, 2H), 6.36 (br s, 1H), 6.43 (br s, 1H), 7.48 (br s, 1H), 7.57 (br s, 1H), 8.35 (s, 1H)	391	Meth 12	
78 [10]	5-Bromo-2-(2-methoxypyrid-5-ylmethylamino)-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.21 (s, 9H), 3.92 (s, 3H), 4.72 (s, 2H), 6.16 (s, 1H), 7.61 (m, 1H), 7.83 (d, 1H), 8.45 (m, 2H)	432	Meth 12	WO 95 / 18097
79 [10]	5-Bromo-2-(3-bromopyrid-5-ylmethylamino)-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.17 (s, 9H), 4.60 (s, 2H), 6.13 (s, 1H), 8.10 (s, 1H), 8.38 (s, 1H), 8.52 (s, 1H), 8.70 (s, 1H)	480	Meth 12	WO 99 / 00385
80 [10]	5-Bromo-2-(fur-2-ylmethylamino)-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.24 (s, 9H), 4.56 (s, 2H), 6.21 (s, 1H), 6.39 (br s, 2H), 7.59 (s, 1H), 8.34 (s, 1H)	391	Meth 12	
81 [10]	5-Bromo-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2-[2-(thien-3-yl)ethylamino] pyrimidine	2.21 (s, 3H), 2.88 (m, 2H), 3.57 (m, 2H), 6.34 (s, 1H), 6.97 (br s, 1H), 7.20 (br s, 1H), 7.49 (m, 1H), 8.33 (s, 1H)	379	Meth 1	
82 [7]	5-Bromo-2-[2-(1-methylpyrrol-2-yl)ethylamino]-4-(5-	2.10 (m, 3H), 2.75 (t, 2H), 3.3-3.4 (m, 5H), 5.80 (s, 1H), 5.87 (s, 1H), 6.37 (m, 1H), 6.60 (s, 1H),	376	Meth 1	Tetrah edron 1999,

	methyl-1*H*-pyrazol-3-ylamino)pyrimidine	7.16 (m, 1H), 8.03 (m, 2H)			55, 11619 - 11640
83	5-Bromo-2-(3-phenylisoxazol-5-ylmethylamino)-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	2.15 (s, 3H), 4.6 (s, 2H), 6.0-6.5 (br s, 1H), 6.75 (br s, 1H), 7.44 (m, 3H), 7.8 (m, 2H), 8.05 (s, 1H)	426	Meth 1	Meth 56
84	5-Bromo-2-[4-(pyrid-2-yl)pyrid-2-ylmethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	2.11 (s, 3H), 4.61 (s, 2H), 6.1 (br s, 1H), 7.42 (t, 1H), 7.98 (m, 4H), 8.00 (s, 1H), 8.60 (d, 1H), 8.67 (d, 1H)	437	Meth 1	Meth 100
85	5-Bromo-2-[5-(pyrid-2-yl)pyrid-3-ylmethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	2.12 (s, 3H), 4.54 (s, 2H), 6.20 (br s, 1H), 7.39 (t, 1H), 7.89 (m, 2H), 8.02 (s, 1H), 8.37 (s, 1H), 8.55 (s, 1H), 8.69 (d, 1H), 9.08 (s, 1H)	437	Meth 1	Meth 102
86	5-Chloro-2-[5-(pyrid-2-yl)pyrid-3-ylmethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	2.12 (s, 3H), 4.54 (s, 2H), 6.20 (br s, 1H), 7.89 (m, 2H), 7.94 (s, 1H), 8.38 (s, 1H), 8.56 (s, 1H), 8.67 (d, 1H), 9.08 (s, 1H)	393	Meth 10	Meth 102
87	5-Bromo-2-(6-chloropyrid-2-ylmethylamino)-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	2.15 (s, 3H), 4.48 (s, 2H), 5.85 (br s, 1H), 7.25 (d, 1H), 7.35 (d, 1H), 7.75 (t, 1H), 8.00 (s, 1H)	394	Meth 1	Meth 94
88	5-Bromo-2-(3-methylpyrid-2-ylmethylamino)-4-(5-methyl-1*H*-pyrazol-3-	2.17 (s, 3H), 2.30 (s, 3H), 4.55 (s, 2H), 6.20 (br s, 1H), 7.20 (t, 1H), 7.55 (d, 1H), 8.03 (s, 1H), 8.35 (d, 1H)	374	Meth 1	Meth 97

	ylamino)pyrimidine				
89	5-Bromo-2-(6-methylpyrid-2-ylmethylamino)-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	2.12 (s, 3H), 2.45 (s, 3H), 4.48 (s, 1H), 6.00 (br s, 1H), 7.08 (d, 2H), 7.55 (t, 1H), 8.00 (s, 1H)	374	Meth 1	Meth 95
90	5-Bromo-2-(5,6-dimethylpyrid-2-ylmethylamino)-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	2.10 (s, 3H), 2.18 (s, 3H), 2.40 (s, 3H), 4.45 (s, 2H), 6.10 (br s, 1H), 7.03 (d, 1H), 7.45 (d, 1H), 7.98 (s, 1H)	388	Meth 1	Meth 96
91	5-Chloro-2-(3-methylisoxazol-5-ylmethylamino)-4-(5-isopropyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.20 (d, 6H), 2.15 (s, 3H), 2.88 (m, 1H), 4.50 (s, 2H), 6.08 (s, 1H), 6.30 (s, 1H), 7.95 (s, 1H)	348	Meth 19	
92	5-Bromo-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2-[1-(pyrid-2-yl)ethylamino] pyrimidine	1.45 (d, 3H), 2.15 (s, 3H), 5.00 (s, 1H), 5.95 (br s, 1H), 7.18 (m, 1H), 7.35 (d, 1H), 7.68 (t, 1H), 7.95 (s, 1H), 8.50 (d, 1H)	374	Meth 1	Meth 91
93	5-Bromo-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2-[1-(pyrid-3-yl)ethylamino] pyrimidine	1.45 (d, 3H), 2.17 (s, 3H), 4.98 (s, 1H), 6.00 (br s, 1H), 7.30 (m, 1H), 7.75 (d, 1H), 7.93 (s, 1H), 8.38 (d, 1H), 8.55 (s, 1H)	374	Meth 1	Meth 90
94	5-Chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2-[1-(pyrid-3-yl)ethylamino] pyrimidine	1.45 (d, 3H), 2.18 (s, 3H), 5.00 (s, 1H), 6.00 (br s, 1H), 7.33 (m, 1H), 7.75 (d, 1H), 7.90 (s, 1H), 8.38 (m, 1H), 8.56 (s, 1H)	330	Meth 10	Meth 90
95	5-Bromo-4-(5-methyl-1*H*-pyrazol-3-ylamino)-	0.88 (t, 3H), 1.85 (m, 2H), 2.18 (s, 3H), 4.80 (s, 1H), 6.00 (br s, 1H),	388	Meth 1	Meth 92

	2-[1-(pyrid-2-yl)propylamino] pyrimidine	7.20 (m, 1H), 7.33 (d, 1H), 7.69 (t, 1H), 7.95 (s, 1H), 8.45 (d, 1H)			
96	5-Chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2-[1-(pyrid-2-yl)propylamino] pyrimidine	0.87 (t, 3H), 1.80 (m, 2H), 2.19 (s, 3H), 4.83 (s, 1H), 6.00 (br s, 1H), 7.18 (m, 1H), 7.33 (d, 1H), 7.67 (t, 1H), 7.87 (s, 1H), 8.47 (d, 1H)	344	Meth 10	Meth 92
97	5-Bromo-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2-[1-(pyrid-3-yl)propylamino] pyrimidine	0.85 (t, 3H), 1.73 (m, 2H), 2.15 (s, 3H), 4.73 (s, 1H), 6.00 (br s, 1H), 7.30 (m, 1H), 7.70 (d, 1H), 7.93 (s, 1H), 8.35 (d, 1H), 8.50 (s, 1H)	388	Meth 1	Meth 93
98	5-Chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)-2-[1-(pyrid-3-yl)propylamino] pyrimidine	0.89 (t, 3H), 1.77 (m, 2H), 2.20 (s, 3H), 4.78 (s, 1H), 6.05 (br s, 1H), 7.30 (t, 1H), 7.75 (d, 1H), 7.85 (s, 1H), 8.38 (d, 1H), 8.52 (s, 1H)	344	Meth 10	Meth 93
99	5-Bromo-2-(3-bromopyrid-5-ylmethylamino)-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.19 (s, 3H), 4.43 (d, 2H), 6.02 (br s, 1H), 7.65 (t, 1H), 7.90 (s, 1H), 8.04 (s, 1H), 8.46 (s, 1H), 8.55 (s, 1H), 12.10 (br s, 1H)	440	Meth 1	WO 99 / 00385
100[11]	5-Bromo-2-[2-(1-methylpyrrol-2-yl)ethylamino]-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.48 (s, 9H), 3.07 (t, 2H), 3.71 (s, 3H), 3.80 (m, 2H), 6.07 (s, 1H), 6.13 (t, 1H), 6.74 (m, 2H), 8.17 (s, 1H)	418	Meth 12	Tetrahedron 1999 (55), 11619 - 11640
101	5-Bromo-2-[2-(pyrimidin-5-yl)ethylamino]-4-(5-*tert*-	1.26 (s, 9H), 2.92 (m, 2H), 3.62 (t, 2H), 6.38 (s, 1H), 8.35 (s, 1H), 8.73 (s, 2H), 9.14 (s, 1H)	417	Meth 12	J Am Chem Soc,

	butyl-1*H*-pyrazol-3-ylamino)pyrimidine				1950, 72, 3539 [12]
102	5-Chloro-2-(pyrid-3-ylmethylamino)-4-(5-propyl-1*H*-pyrazol-3-ylamino)pyrimidine	0.84 (t, 3H), 1.50 (m, 2H), 2.45 (m, 2H), 4.46 (s, 2H), 6.18 (br s, 1H), 7.30 (t, 1H), 7.67 (d, 1H), 7.91 (s, 1H), 8.38 (d, 1H), 8.48 (s, 1H)	344	Meth 16	
103	5-Chloro-4-(5-isopropyl-1*H*-pyrazol-3-ylamino)-2-(pyrid-3-ylmethylamino) pyrimidine	1.13 (d, 6H), 2.84 (m, 1H), 4.47 (s, 2H), 6.24 (br s, 1H), 7.29 (t, 1H), 7.65 (d, 1H), 7.92 (s, 1H), 8.39 (d, 1H), 8.49 (s, 1H)	344	Meth 19	
104	5-Bromo-2-[3-(methoxycarbonyl)isoxazol-5-ylmethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	2.17 (s, 3H), 3.84 (s, 3H), 4.59 (s, 2H), 6.21 (br s, 1H), 6.58 (s, 1H), 8.03 (s, 1H)	408	Meth 1	Meth 74 [13]
105	5-Bromo-2-[3-(pyrrolidin-1-ylcarbonyl)isoxazol-5-ylmethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	1.86 (m, 4H), 2.18 (s, 3H), 3.44 (t, 2H), 3.57 (t, 2H), 4.58 (s, 2H), 6.20 (br s, 1H), 6.44 (s, 1H), 8.04 (s, 1H)	447	Meth 1	Meth 78
106	5-Bromo-2-[3-(hydroxymethyl)isoxazol-5-ylmethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine	2.17 (s, 3H), 4.40 (s, 2H), 4.50 (s, 2H), 6.17 (s, 1H), 6.28 (br s, 1H), 8.02 (s, 1H)	380	Meth 1	Meth 76

[1] Heated for 12 hours.

[2] Heated for 24 hours.

[3] Reaction treated with 2M NH_3/MeOH to pH 9. Precipitate was filtered and washed with distilled water and diethyl ether.

[4] No aqueous work-up, product precipitates from DCM.

[5] No chromatography necessary.

[6] 500MHz (393K).

[7] NMR run with no d4 acetic acid.

[8] NMR run at 373K/400MHz.

[9] NMR run with no d4 acetic acid at 343K.

[10] NMR: Trifluorodeuterated acetic acid-d_1 use in place of acetic aicd-d_4.

[11] NMR run in CD_3OD.

[12] Compound could be prepared by the procedure described in this paper.

[13] Ester exchange with the methanol used in the chromatography occurred.

Example 107

5-Bromo-2-(3-carbamoylisoxazol-5-ylmethylamino)-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine

5-Bromo-2-[3-(methoxycarbonyl)isoxazol-5-ylmethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine (Example 104; 50mg, 0.11mmol) was suspended in 7N methanolic ammonia (5ml) and stirred at ambient temperature for 18 hours. The volatiles were removed by evaporation and the residue was triturated with DCM/diethyl ether (50:50) and the product collected by filtration to give the title compound (35mg, 76%). NMR (DMSO): 2.18 (s, 3H), 4.57 (d, 2H), 6.28 (br s, 1H), 6.50 (s, 1H), 7.72 (s, 2H), 8.01 (s, 1H), 8.05 (s, 1H), 12.06 (s, 1H); m/z 393 $(MH)^+$.

Preparation of Starting Materials :-

The starting materials for the examples above are either commercially available or are readily prepared by standard methods from known materials. For example, the following reactions are an illustration, but not a limitation, of some of the starting materials used in the above reactions.

Method 1

5-Bromo-2-chloro-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine

A solution of 5-bromo-2,4-dichloropyrimidine (10.0g, 44mmol), 3-amino-5-methyl-1*H*-pyrazole (6.0g, 62mmol) and *N*,*N*-diisopropylethylamine (9.20ml, 53mmol) in 1-butanol (80ml) was heated at 85ºC for 12 hours. The mixture was allowed to cool to ambient temperature and the resulting precipitate collected by filtration. The solid product was washed with ethanol and dried to give the sub-titled compound (10.8g, 85%). ^{1}H NMR (DMSO): δ 2.23 (s, 3H), 6.23 (s, 1H), 8.39 (s, 1H), 9.21 (s, 1H), 12.27 (s, 1H); MS: m/z 290 $(MH)^+$.

Method 2

2-Oxobutylnitrile

Acetonitrile (13.7ml, 260mmol) was added to a suspension of sodium hydride (10.4g of a 60% suspension in mineral oil, 260mmol) in ethyl propionate (22.3g, 220mmol) and anhydrous 1,4-dioxane (200ml) at ambient temperature. The mixture was heated at 100ºC for 12 hours and then allowed to cool. Water was added, the mixture adjusted to pH 2.0 with concentrated hydrochloric acid and extracted with DCM. The extracts were combined dried ($MgSO_4$) and the volatiles removed by evaporation. The residue was purified by column chromatography on silica gel eluting with DCM to give the title compound (20g, 94%) as an oil. NMR ($CDCl_3$): 1.10 (t, 3H), 2.65 (q, 2H), 3.50 (s, 2H).

Methods 3 - 5

The following compounds were prepared by the procedure of Method 2 using the appropriate starting materials.

Method	**Compound**
3	2-Cyclopropyl-2-oxoethylnitrile
4	2-Oxopentylnitrile
5	2-Oxo-3-methylbutylnitrile

Method 6

3-Amino-5-ethyl-1*H*-pyrazole

Hydrazine monohydrate (11.3g, 230mmol) was added to a solution of 3-oxobutyronitrile (Method 2; 20.0g, 210mmol) in ethanol (50ml) and the mixture heated at 70ºC for 12 hours. The volatiles were removed by evaporation and the residue was purified by column chromatography on silica gel eluting with DCM/methanol (90:10) to give the title compound

as an oil. (10.2g, 44%). NMR (DMSO): 1.10 (t, 3H), 2.40 (q, 2H), 5.15 (s, 1H); m/z 112 $(MH)^+$.

Methods 7 - 9

The following compounds were prepared by the procedure of Method 6 using the appropriate starting materials.

Method	Compound	SM
7	3-Amino-5-cyclopropyl-1*H*-pyrazole	Method 3
8	3-Amino-5-propyl-1*H*-pyrazole	Method 4
9	3-Amino-5-isopropyl-1*H*-pyrazole	Method 5

Method 10

2,5-Dichloro-4-(5-methyl-1*H*-pyrrazol-3-ylamino)pyrimidine

A solution of 2,4,5-trichloropyrimidine (6.0g, 32.6mmol), 3-amino-5-methyl-1*H*-pyrrazole (3.18g, 32.7mmol) and *N*,*N*-diisopropylethylamine (6.30ml, 36.2mmol) in 1-butanol (50ml) was heated at 100ºC for 2 hours. The volatiles were removed by evaporation and the residue was triturated with DCM to afford the title compound (5.7g, 72%) as a white solid. NMR (DMSO): 2.23 (s, 3H), 6.23 (s, 1H), 8.39 (s, 1H), 9.21 (s, 1H), 12.27 (s, 1H); m/z 290 $(MH)^+$.

Methods 11 - 21

The following compounds were prepared by the procedure of Method 10 using the appropriate starting materials.

Meth	Compound	SM
11	5-Bromo-2-chloro-4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrimidine	Meth 7
12	5-Bromo-2-chloro-4-(5-*tert*-butyl-1H-pyrazol-3-ylamino)pyrimidine	
13	2,5-Dichloro-4-(5-*tert*-butyl-1H-pyrazol-3-ylamino)pyrimidine	
14	5-Bromo-2-chloro-4-(5-ethyl-1H-pyrazol-3-ylamino)pyrimidine	Meth 6
15	4-(5-Methyl-1*H*-pyrazol-3-ylamino)-2-chloropyrimidine	
16	2,5-Dichloro-4-(5-propyl-1*H*-pyrazol-3-ylamino)pyrimidine	Meth 8
17	2,5-Dichloro-4-(5-ethyl-1*H*-pyrazol-3-ylamino)pyrimidine	Meth 6
18	5-Bromo-4-(5-propyl-1*H*-pyrazol-3-ylamino)-2-chloropyrimidine	Meth 8

19	2,5-Dichloro-4-(5-isopropyl-1*H*-pyrazol-3-ylamino)pyrimidine	Meth 9
20	2,5-Dichloro-4-(5-cyclopropyl-1*H*-pyrazol-3-ylamino)pyrimidine	Meth 7
21	5-Bromo-4-(5-isopropyl-1*H*-pyrazol-3-ylamino)-2-chloropyrimidine	Meth 9

Method 22

α-Chlorobenzaldehyde oxime

N-chlorosuccinimide (5.50g, 41.3mmol) was added in portions to a solution of benzaldehyde oxime (5.0g, 41.3mmol) in DMF (34ml) such that the temperature did not rise above 35ºC. The mixture was stirred at ambient temperature for 2 hours and then cooled with an ice bath. Water was added and the aqueous mixture extracted with ether. The organics were combined, washed with water and brine, dried ($MgSO_4$) and the solvent removed by evaporation to give the title compound (6.43g, 100%) as an oil. NMR ($CDCl_3$): 7.4 (m, 3H), 7.8 (d, 2H), 8.9 (bs, 1H).

Methods 23 - 33

The following compounds were prepared by the procedure of Method 22 using the appropriate starting materials.

Method	Compound	SM
23	1-chloro-2-methylpropylaldehyde oxime	
24	α-Chloro-2-methoxybenzaldehyde oxime	
25	α-Chloro-2-chlorobenzaldehyde oxime	Method 36
26	α-Chloro-2-fluorobenzaldehyde oxime	Method 37
27	α-Chloro-2-trifluoromethoxybenzaldehyde oxime	Method 38
28	α-Chloro-2-ethoxybenzaldehyde oxime	Method 39
29	α-Chloro-2-trifluoromethylbenzaldehyde oxime	Method 40
30	α-Chloro-2-methylbenzaldehyde oxime	Method 41
31	α-Chloro-2-bromobenzaldehyde oxime	
32	α-Chloro-2-methoxypyrid-3-ylcarbaldehyde oxime	J.Chem. Soc. Perkin Trans 1 1990 2409-15.
33	α-Chloro-3-methoxybenzaldehyde oxime	Method 35

Method 34

α-Chloro-pyrid-3-ylcarbaldehyde oxime was prepared according to the method described in Tetrahedron 2000, 56, 1057-1064.

Method 35

3-Methoxybenzaldehyde oxime

A solution of hydroxylamine hydrochloride (10g, 0.144mol) in distilled water (20ml) was added to 20%(w/v) aqueous sodium hydroxide solution (28ml). 3-Methoxybenzaldehyde (14ml, 0.12mol) was added in one portion and the mixture was stirred for 2 hours at 0-5ºC. The mixture was adjusted to pH7 and extracted with dichloromethane. The extracts were combined, dried ($MgSO_4$) and the solvent removed by evaporation to give the title compound (18.7g, 100%) as a colourless oil. NMR ($CDCl_3$): 3.8 (s, 3H), 6.9 (m, 1H), 7.1 (m, 2H), 7.15 (m, 1H), 8.1 (s, 1H), 8.6 (br s, 1H).

Methods 36 - 42

The following compounds were prepared by the procedure of Method 35 using the appropriate starting materials.

Method	Compound
36	2-chlorobenzaldehyde oxime
37	2-fluorobenzaldehyde oxime
38	2-trifluoromethoxybenzaldehyde oxime
39	2-ethoxybenzaldehyde oxime
40	2-trifluoromethylbenzaldehyde oxime
41	2-methylbenzaldehyde oxime
42	2-iodobenzaldehyde oxime

Method 43

5-(*tert*-Butoxycarbonylaminomethyl)-3-phenylisoxazole

A solution of α-chlorobenzaldehyde oxime (Method 22; 1g, 6.4mmol) in THF (13ml) was added dropwise to a solution of *N*-*tert*-butoxycarbonyl-propargylamine (0.5g, 3.2mmol) and triethylamine (0.9ml, 6.4mmol) in THF (25ml) cooled with an ice bath. The mixture was allowed to warm to ambient temperature and stirred for 2 days. The volatiles were removed by evaporation and the residue dissolved in DCM. The solution was washed with water and brine, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was triturated with

isohexane/ether (9:1) and collected by filtration to give the title compound (473mg, 54%). NMR ($CDCl_3$) 1.45 (s, 9H), 4.45 (d, 2H), 5.10 (bs, 1H), 6.5 (s, 1H), 7.42 (m, 3H), 7.8 (m, 2H).

Methods 44 - 55

The following compounds were prepared by the procedure of Method 43 using the appropriate starting materials.

Meth	Compound	SM
44	5-(*tert*-Butoxycarbonylaminomethyl)-3-isopropylisoxazole	Meth 23
45	5-(*tert*-Butoxycarbonylaminomethyl)-3-(2-methoxyphenyl)isoxazole	Meth 24
46	5-(*tert*-Butoxycarbonylaminomethyl)-3-(2-chlorophenyl)isoxazole	Meth 25
47	5-(*tert*-Butoxycarbonylaminomethyl)-3-(2-fluorophenyl)isoxazole	Meth 26
48	5-(*tert*-Butoxycarbonylaminomethyl)-3-(2-trifluoromethoxyphenyl)isoxazole	Meth 27
49	5-(*tert*-Butoxycarbonylaminomethyl)-3-(2-ethoxyphenyl)isoxazole	Meth 28
50	5-(*tert*-Butoxycarbonylaminomethyl)-3-(2-trifluoromethylphenyl)isoxazole	Meth 29
51	5-(*tert*-Butoxycarbonylaminomethyl)-3-(2-methylphenyl)isoxazole	Meth 30
52	5-(*tert*-Butoxycarbonylaminomethyl)-3-(2-bromophenyl)isoxazole	Meth 31
53	5-(*tert*-Butoxycarbonylaminomethyl)-3-(2-methoxypyrid-3-yl)isoxazole	Meth 32
54	5-(*tert*-Butoxycarbonylaminomethyl)-3-(3-methoxyphenyl)isoxazole	Meth 33
55	5-(*tert*-Butoxycarbonylaminomethyl)-3-(pyrid-3-yl)isoxazole	Meth 34

Method 56

5-Aminomethyl-3-phenylisoxazole

Trifluoroacetic acid (1.7ml, 2.6mmol) was added dropwise to a solution of 5-(*tert*-butoxycarbonylaminomethyl)-3-phenylisoxazole (Method 43; 473mg, 1.73mmol) in DCM (8ml) cooled in an ice bath. The mixture was warmed to ambient temperature and stirred for 18 hours and the volatiles removed by evaporation. The residue was triturated with ether to give the title compound (427mg, 86%). NMR (DMSO) 4.33 (s, 2H), 7.1 (s, 1H), 7.5 (m, 3H), 7.8 (m, 2H), 8.6 (br s, 3H).

Methods 57 - 68

The following compounds were prepared by the procedure of Method 56 using the appropriate starting materials.

Method	Compound	Method
57	5-Aminomethyl-3-isopropylisoxazole	Method 44
58	5-Aminomethyl-3-(2-methoxyphenyl)isoxazole	Method 45
59	5-Aminomethyl-3-(2-chlorophenyl)isoxazole	Method 46
60	5-Aminomethyl-3-(2-fluorophenyl)isoxazole	Method 47
61	5-Aminomethyl-3-(2-trifluoromethoxyphenyl)isoxazole	Method 48
62	5-Aminomethyl-3-(2-ethoxyphenyl)isoxazole	Method 49
63	5-Aminomethyl-3-(2-trifluoromethylphenyl)isoxazole	Method 50
64	5-Aminomethyl-3-(2-methylphenyl)isoxazole	Method 51
65	5-Aminomethyl-3-(2-bromophenyl)isoxazole	Method 52
66	5-Aminomethyl-3-(2-methoxypyrid-3-yl)isoxazole	Method 53
67	5-Aminomethyl-3-(3-methoxyphenyl)isoxazole	Method 54
68	5-Aminomethyl-3-(pyrid-3-yl)isoxazole	Method 55

Method 69

5-(*tert*-Butoxycarbonylaminomethyl)-3-(pyrid-2-yl)isoxazole

Sodium hypochlorite (16ml of a 14%w/v aqueous solution, 29.5mmol) was added dropwise to a solution of 2-pyridinealdoxime (2g, 16.4mmol) and *N*-*tert*-butoxycarbonyl-propargylamine (5.6g, 36.1mmol) in DCM (30ml) cooled in an ice bath. The mixture was stirred vigorously and allowed to warm to ambient temperature and stirred for 18 hours. The aqueous layer was separated and extracted with DCM. The combined organic extracts were combined, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography on silica gel eluting with diethyl ether/isohexane (1:1) to give the title compound (1.93g, 43%). NMR ($CDCl_3$) 1.45 (s, 9H), 4.5 (m, 2H), 5.03 (bs, 1H), 6.8 (s, 1H), 7.35 (m, 1H), 7.8 (m, 1H), 8.05 (d, 1H), 8.67 (m, 1H).

Method 70

5-Aminomethyl-3-(pyrid-2-yl)isoxazole

5-(tert-Butoxycarbonylaminomethyl)-3-(pyrid-2-yl)isoxazole (Method 69) was treated as described in Method 56 to give 5-aminomethyl-3-(2-pyridyl)isoxazole. NMR (DMSO) 4.38 (s, 2H), 7.1 (s, 1H), 7.5 (m, 1H), 7.95 (m, 2H), 8.65 (br s, 3H), 8.7 (m, 1H).

Method 71

3-Methyl-5-(1-phthalamidoethyl)isoxazole

A solution of triethylamine (0.35ml, 2.5mmol) in toluene (15ml) was added dropwise to a solution of phenylisocyanate (5.43ml, 50mmol), nitroethane (2.15ml, 30mmol) and N-(but-1-yn-3-yl)phthalamide (5.0g, 25mmol) in toluene (65ml) at ambient temperature. The mixture was stirred for 18 hours, filtered and the volatiles removed by evaporation. The residue was triturated with ether and the product collected by filtration to give the title compound (5.35g, 89%). NMR ($CDCl_3$): 1.88 (d, 3H), 2.27 (s, 3H), 5.60 (q, H), 6.11 (s, H), 7.69-7.75 (m, 2H), 7.79-7.85 (m, 2H); m/z 257 $(MH)^+$.

Method 72

5-(1-aminoethyl)-3-methylisoxazole

A mixture of the 3-methyl-5-(1-phthalamidoethyl)isoxazole (Method 71; 3.55g, 13.9mmol), hydrazine monohydrate (0.75ml, 15.3mmol) and ethanol (50ml) was heated at reflux for 4 hours. The mixture was allowed to cool to ambient temperature and glacial acetic acid (8.8ml, 153mmol) added, the mixture then heated at reflux for 2 hours. The mixture was allowed to cool to ambient temperature and the mixture neutralized with 50% aqueous sodium hydroxide solution, diluted with water and extracted with DCM, and the combined extracts washed with water followed by brine. The organics were separated, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was dissolved in ethanol and treated with an excess of 1N ethereal hydrogen chloride, the volatiles removed by evaporation to give the title compound (1.52g, 87%). NMR (DMSO): 1.46 (dd, 3H), 2.20 (m, 3H), 4.39 (q H), 6.38 (s, 1H), 6.60 (br s, 3H); m/z 127 $(MH)^+$.

Method 73

3-Ethoxycarbonyl-5-[N-(tert-butyloxycarbonyl)aminomethyl]isoxazole

A solution of ethyl chlorooximidoacetate (10g, 66mmol) in THF (200ml) was added dropwise over 3 hours to a mixture of N-(tert-butyloxycarbonyl)propargylamine (20.5g, 131mmol) and triethylamine (11.2ml, 80mmol) in tetrahyrofuran (100ml). The mixture was stirred at ambient temperature for 18 hours and then the volatiles were removed by evaporation. The residue was dissolved in DCM and washed with water followed by brine. The organics were separated, dried ($MgSO_4$) and the solvent removed by evaporation. The residue was purified by column chromatography on silica gel eluting with isohexane/diethyl

ether (80:20 then 50:50) to give the title compound (10.6g, 60%). NMR (DMSO): 1.3 (t, 3H), 1.38 (s, 9H), 4.35 (m, 2H), 6.62 (s, 1H), 7.55 (s, 1H); m/z 269 $(M-H)^-$.

Method 74

3-Ethoxycarbonyl-5-aminomethylisoxazole

Trifluoroacetic acid (2.1ml, 29mmol) was added to a solution of 3-ethoxycarbonyl-5-[N-(tert-butyloxycarbonyl)aminomethyl]isoxazole (Method 73; 790mg, 2.9mmol) in DCM (15ml). The mixture was stirred at ambient temperature for 4 hours then the volatiles removed by evaporation. The residue was triturated with diethyl ether to give the title compound (763g, 93%). NMR (DMSO): 1.31 (t, 3H), 4.37 (m, 2H), 6.97 (s, 1H), 8.64 (s, 3H); m/z 171 $(MH)^+$.

Method 75

3-Hydroxymethyl-5-[N-(tert-butyloxycarbonyl)aminomethyl]isoxazole

Sodium borohydride (610mg, 16mmol) was added in portions to a solution of 3-ethoxycarbonyl-5-[*N*-(tert-butyloxycarbonyl)aminomethyl]isoxazole (Method 73; 1.62g, 6mmol) in ethanol (15ml) at 0ºC under a nitrogen atmosphere. The mixture was stirred at ambient temperature for 4 hours then quenched with saturated aqueous sodium hydrogen carbonate solution. The mixture was extracted with EtOAc and the organics washed with brine then dried ($MgSO_4$). The solvent was removed by evaporation to give the title compound (1.25g, 91%). NMR (DMSO): 1.38 (s, 9H), 4.21 (d, 2H), 4.44 (s, 2H), 5.40 (br s, 1H), 6.21 (s, 1H), 7.49 (br s, 1H); m/z 229 $(MH)^+$.

Method 76

3-Hydroxymethyl-5-aminomethylisoxazole

Trifluoroacetic acid (4ml, 54mmol) was added to a solution of 3-hydroxymethyl-5-[N-(tert-butyloxycarbonyl)aminomethyl]isoxazole (Method 75; 1.25g, 5.4mmol) in DCM (40ml). The mixture was stirred at ambient temperature for 18 hours then the volatiles removed by evaporation. The residue was purified by chromatography on a SCX-2 column (50g) eluting with methanol then 7N ammonia in methanol to give the title compound (676mg, 96%). NMR (DMSO): 1.97 (br s, 2H), 3.76 (s, 2H), 4.44 (s, 2H), 5.38 (s, 1H), 6.26 (s, 1H).

Method 77

3-(Pyrrolidin-1-ylcarbonyl)-5-[N-(tert-butyloxycarbonyl)aminomethyl]isoxazole

3-Ethoxycarbonyl-5-[N-(tert-butyloxycarbonyl)aminomethyl]isoxazole (Method 73; 500mg, 1.85mmol) was dissolved in pyrrolidine (4ml) and the mixture heated for 3 hours at 85ºC. The volatiles were removed by evaporation and the residue was triturated with diethyl ether to give the title compound (432mg, 79%) as a white solid. NMR (DMSO): 1.38 (s, 9H), 1.85 (m, 4H), 3.50 (t, 2H), 3.62 (t, 2H), 4.29 (d, 2H), 6.47 (1H), 7.53 (s, 1H); m/z 240 $(M-C_4H_8)^+$.

Method 78

3-(Pyrrolidin-1-ylcarbonyl)-5-aminomethyl]isoxazole

3-(Pyrrolidin-1-ylcarbonyl)-5-[N-(tert-butyloxycarbonyl)aminomethyl]isoxazole (Method 77) was deprotected as described in Method 74 to give the title compound as its trifluoroacetate salt (428mg, 95%). NMR (DMSO): 1.88 (m, 4H), 3.49 (t, 2H), 3.63 (t, 2H), 4.35 (s, 2H), 6.83 (s, 1H), 8.58 (s, 3H); m/z 196 $(MH)^+$.

Method 79

5-[N-(tert-Butoxycarbonyl)aminomethyl]-3-(2-iodoophenyl)isoxazole

2-Iodobenzaldehyde oxime (Method 42) was treated as described in Methods 22 and 43 to give the title compound.

Method 80

5-[N-(*tert*-Butoxycarbonyl)aminomethyl]-3-(2-cyanophenyl)isoxazole

Copper (I) cyanide (2.49g, 27.8mmol), *tetra*-n-butylammoniumcyanide (1.87g, 6.95mmol), tris(dibenzylideneacetone)dipalladium(0) (0.247g, 0.28mmol) and diphenylphosphinoferrocene (0.619g, 1.12mmol) were added to a degassed solution of 5-[N-(*tert*-butoxycarbonyl)aminomethyl]-3-(2-iodoophenyl)isoxazole (Method 79; 2.78g, 6.95mmol) in 1,4-dioxan (35ml) under nitrogen. The mixture was heated at reflux for 3 hours, cooled to ambient temperature, diluted with EtOAc and filtered through diatomaceous earth. The filtrate was washed with saturated aqueous sodium hydrogen carbonate solution and brine, dried ($MgSO_4$) and the solvent was removed by evaporation. The residue was purified by column chromatography on silica gel eluting with EtOAc/isohexanes (15:85 increasing in polarity to 25:75) to give the title compound (1.29g, 62%). NMR ($CDCl_3$): 1.49 (s, 9H), 4.52 (d, 2H), 5.09 (br s, H), 6.81 (s, H), 7.55 (t, H), 7.70 (t, H), 7.79 (d, H), 7.95 (d, H); m/z 300 $(MH)^+$.

Method 81

5-Aminomethyl-3-(2-cyanophenyl)isoxazole

5-[N-(*tert*-Butoxycarbonyl)aminomethyl]-3-(2-cyanophenyl)isoxazole (Method 80; 1.28g, 4.28mmol) was treated as described in Method 56 to give the title compound (1.34g, 100%). NMR (DMSO): 4.45 (s, 2H), 7.17 (s, H), 7.73 (dd, H), 7.85-7.95 (m, 2H), 8.62 (br s, 3H); m/z 200 $(MH)^+$.

Method 82

3-Methyl-5-{2-[*bis*-(N-*tert*-butoxycarbonyl)amino]ethyl}isoxazole

Bis-N-*tert*-butoxycarbonyl-3-butyne as synthesised in *J. Am. Chem. Soc*. 1987 (109), 2765 (2.2g, 8.2mmol), was treated as described in Method 71 to give the title compound (0.59g, 22%). NMR ($CDCl_3$): 1.49 (s, 18H), 2.24 (s, 3H), 3.00 (t, 2H), 3.88 (t, 2H), 5.85 (s, H).

Method 83

3-Methyl-5-(2-aminoethyl)isoxazole

Trifluoroacetic acid (2.5ml, 3.8mmol) was added dropwise to a solution of 3-methyl-5-{2-[*bis*-(N-*tert*-butoxycarbonyl)amino]ethyl}isoxazole (Method 82; 0.589g, 1.8mmol) in DCM (10ml) cooled at 0ºC. The mixture was allowed to warm to ambient temperature and stirred for 48 hours. The volatiles were removed by evaporation and the residue was purified

by chromatography on a SCX-2 ion exchange column eluting with methanol and then 7 N ammonia in methanol. The purified product was treated with an excess of 1.0M ethereal hydrogen chloride (3.5ml) to give the title compound as its hydrochloride salt (0.24g, 82%). NMR (DMSO) freebase: 2.18 (s, 3H), 2.71-2.79 (m, 2H), 2.80-2.88 (m, 2H), 6.10 (s, H).

Method 84

3-Azidomethyl-5-methylisoxazole

3-Chloromethyl-5-methylisoxazole (500mg, 3.8mmol) and sodium azide (494mg, 7.6mmol) were heated in DMF (10ml) at 60ºC for 6 hours. The reaction mixture was diluted with water then extracted with EtOAc. The organic extracts were dried ($MgSO_4$) and the volatiles removed by evaporation to give the title compound (387mg, 73%) as an oil. NMR (DMSO): 2.40 (s, 3H), 4.48 (s, 2H), 6.28 (s, 1H).

Method 85

3-Aminomethyl-5-methylisoxazole

3-Azidomethyl-5-methylisoxazole (Method 84; 384mg, 2.8mmol) and polystyrene polymer supported triphenylphosphine (4.2g, 4.2mmol) were stirred together in a mixture of THF (17ml) and distilled water (0.58ml) for 24 hours. The reaction mixture was filtered, the resin washed with diethyl ether and then DCM. The combined filtrates were evaporated and the residue purified on a SCX-2 column eluting with methanol followed by 7N methanolic ammonia to give the title compound (211mg, 67%) as an oil. NMR (DMSO): 1.93 (br s, 2H), 2.34 (s, 3H), 3.63 (s, 2H), 6.17 (s, 1H).

Method 86

α-Methyl-pyridin-3-ylcarbaldehyde oxime

Hydroxylamine hydrochloride (9.46g, 136.2mmol) was added to a solution of 3-acetylpyridine (11.02g, 90.7mmol) in methanol (100ml) and the reaction mixture heated at reflux for 30 minutes. The volatiles were removed by evaporation and the residue dissolved in water. The solution was cooled to 0ºC and basified with 2N aqueous sodium hydroxide solution to pH 12 and the mixture then extracted with EtOAc. The extracts were combined, washed with saturated brine and dried (Na_2SO_4). The solvent was removed by evaporation to give the title product (11.6g, 94%) as a solid. NMR (DMSO): 2.20 (s, 3H), 7.40 (m, 1H), 8.00 (m, 1H), 8.55 (d, 1H), 8.85 (s, 1H) 11.43 (s, 1H). m/z: 137 $(MH)^+$.

Methods 87 - 89

The following compounds were prepared by the procedure of Method 86 using the appropriate starting materials.

Method	Compound
87	α-Methyl-pyridin-2-ylcarbaldehyde oxime
88	α-Ethyl-pyridin-2-ylcarbaldehyde oxime
89	α-Ethyl-pyridin-3-ylcarbaldehyde oxime

Method 90

3-(1-Aminoethyl)pyridine

A 50% suspension of rainey nickel in water (1.1g) was added to a solution of α-methyl-pyridin-3-ylcarbaldehyde oxime (Method 86; 10.6g, 77.9mmol) and 20% ethanolic ammonia (500ml) and the reaction mixture hydrogenated with gaseous hydrogen at 40 psi and 40ºC until the theoretical volume of gas was consumed. The reaction mixture was filtered through a layer of diatomaceous earth and the filter pad washed with water and ethanol. The filtrate was removed by evaporation of give the title product. (8.05g, 85%) as an oil. NMR (DMSO): 1.28 (d, 3H), 4.05 (m, 1H), 7.33 (t, 1H), 7.75 (d, 1H), 8.40 (d, 1H), 8.55 (s, 1H). m/z: 123 $(MH)^+$.

Methods 91 - 93

The following compounds were prepared by the procedure of Method 90 using the appropriate starting materials.

Method	Compound	SM
91	2-(1-Aminoethyl)pyridine	Method 87
92	2-(1-Aminopropyl)pyridine	Method 88
93	3-(1-Aminopropyl)pyridine	Method 89

Method 94

2-Aminomethyl-6-chloropyridine

A 1M solution of lithium aluminium hydride in THF (2.88ml, 2.88mmol) was added dropwise to a solution of 6-chloro-2-cyanopyridine (532mg, 3.84mmol) in THF (10ml) at -5ºC under an atmosphere of nitrogen. The mixture was stirred at -5ºC for two hours and the reaction quenched by careful, sequential addition of water (0.1ml), 15% aqueous sodium

hydroxide solution (0.1ml) and then water (0.3ml). The mixture was stirred for one hour at 0ºC, the insolubles removed by filtration and the filter pad washed thoroughly with methanol. The resulting solution was evaporated and the residue purified by column chromatography on silica gel eluting with DCM/methanol/ammonia (95:5:0 increasing in polarity to 90:10:1) to give the title compound. (215mg, 40%) as an oil. NMR (DMSO): 2.10 (br s, 2H), 3.75 (s, 2H), 7.30 (d, 1H), 7.55 (d, 1H), 7.80 (t, 1H).

Methods 95 - 97

The following compounds were prepared by the procedure of Method 94 using the appropriate starting materials.

Method	Compound
95	2-Aminomethyl-6-methylpyridine
96 [1]	2-Aminomethyl-5,6-dimethylpyridine
97	2-Aminomethyl-3-methylpyridine

[1] SM Bioorg. Med. Chem. Lett. 1998, 453-8

Method 98

2-(*N*-Oxopyridin-4-yl)pyridine

3-Chloroperbenzoic acid (57%-86% active strength) (7.5g, 43mmol) was added in portions to a solution of 2-(pyridin-4-yl)pyridine (4.78g, 30.6mmol) in DCM (50ml) at 0ºC. After stirring for 2 hours sodium metabisulfite was added in portions until all excess peroxide was destroyed. The solids were removed by filtration and the filtrate was basified with solid potassium carbonate. The mixture was filtered, the filtrate evaporated and the residue purified by column chromatography on silica gel eluting with methanol/acetone (10:90) to give the title compound (4.2g, 80%) as a white solid. NMR (DMSO): 7.41 (t, 1H), 7.92 (t, 1H), 8.10 (m, 3H), 8.30 (d, 2H), 8.70 (d, 1H); m/z 173 $(MH)^+$.

Method 99

2-(2-Cyanopyridin-4-yl)pyridine

Trimethylsilylcyanide (1.9ml, 14.5mmol) was added dropwise to a suspension of 2-(*N*-oxopyridin-4-yl)pyridine (Method 98; 1g, 5.8mmol) and triethylamine (1.2ml, 8.7mmol) in acetonitrile (5ml). The mixture was heated at 110ºC for 18 hours, cooled to ambient temperature then diluted with aqueous saturated sodium hydrogen carbonate solution. The

mixture was extracted with DCM, the extracts dried ($MgSO_4$) and the volatiles removed by evaporation. The residue was pre-adsorbed onto silica and purified by column chromatography on silica gel eluting with hexane:EtOAc (1:1). The purified product was triturated with diethyl ether to give the title compound (627mg, 60%) as a white solid. NMR (DMSO): 7.54 (t, 1H), 8.01 (t, 1H), 8.25 (d, 1H), 8.40 (d, 1H), 8.66 (s, 1H), 8.77 (d, 1H), 8.87 (d, 1H).

Method 100

2-(2-Aminomethylpyridin-4-yl)pyridine

2-(2-Cyanopyridin-4-yl)pyridine (Method 99; 563mg, 3.11mmol) was dissolved in anhydrous THF (10ml) under a nitrogen atmosphere and was cooled to 0ºC. $LiAlH_4$ (2.3ml of a 1M solution in THF, 2.3mmol) was added dropwise and the reaction was stirred at 0ºC for 3 hours. The reaction was quenched with water (0.1ml) followed by 15% sodium hydroxide solution (0.1ml) then water (0.3ml). The mixture was filtered and the filter pad was washed with methanol. The volatiles were removed from the filtrate by evaporation to give the title compound (570mg, 99%) as a gum. m/z 186 $(MH)^+$

Method 101

2-(3-Cyanopyridin-5-yl)pyridine

2-(3-Bromopyridin-5-yl)pyridine (2g, 10.9mmol) in THF (10ml) was added dropwise to a solution of 2-pyridylzincbromide (22ml of a 0.5M solution in THF, 11mmol) in THF (10ml) under a nitrogen atmosphere. Tetrakis (triphenylphosphine)palladium(0) (630mg, 0.54mmol) was added and the reaction stirred at ambient temperature for 18 hours. The reaction was quenched with saturated aqueous ammonium chloride solution then the volatiles were removed by evaporation. The residue was suspended in water then extracted with DCM. The organic extracts were combined, washed with water then filtered through phase separating paper and the volatiles removed by evaporation. The residue was purified by column chromatography on silica gel eluting with hexane:EtOAc (2:1). The purified product was triturated with diethyl ether to give the title compound (0.98g, 50%) as a white solid. NMR (DMSO): 7.47 (t, 1H), 7.97 (t, 1H), 8.15 (d, 1H), 8.75 (d, 1H), 8.90 (d, 1H), 9.07 (s, 1H), 9.53 (s, 1H); m/z 182 $(MH)^+$.

Method 102

2-(3-Aminomethylpyridin-5-yl)pyridine

2-(3-Cyanopyridin-5-yl)pyridine (Method 101; 0.98g, 5.4mmol) was dissolved in a mixture of ethanol (45ml) and methanol (30ml). Concentrated hydrochloric acid (1.2ml) and 10% palladium on carbon catalyst (575mg) were added and the mixture stirred under an atmosphere of hydrogen for 4 hours. The mixture was filtered through diatomaceous earth, the filter pad washed with ethanol and the volatiles removed from the filtrate by evaporation. The crude solid was suspended in a small volume of methanol and filtered to give the title compound (794mg, 66%) as an orange solid. NMR (DMSO): 4.31 (m, 2H) 7.58 (t, 1H), 8.09 (t, 1H), 8.24 (d, 1H), 8.78 (d, 1H), 8.89 (bs, 2H), 9.03 (s, 1H), 9.26 (s, 1H), 9.43 (s, 1H); m/z 186 $(MH)^+$.

Pharmacological Analysis

Methods For Detecting Inhibition Of Igf-1r Kinase Activity And Downstream Signalling And Selectivity Over Insulin Receptor Kinase And Egfr Signalling

Abbreviations used

PBS (PBS/T) is Phosphate buffered saline, pH7.4 (with 0.05% Tween 20)

HEPES is *N*-[2-Hydroxyethyl]piperazine-*N*'-[2-ethanesulfonic acid]

DTT is dithiothreitol

TMB is tetramethyl benzidine

DMSO is dimethyl sulphoxide

BSA is bovine serum albumin

ATP is adenosine tri-phosphate

DMEM is Dulbecco's modified Eagle's Medium

FBS/FCS is foetal bovine/calf serum

HBSS is Hanks Balanced Salts Solution

HRP is horse-radish peroxidase

SDS is sodium dodecyl sulphate

IGF-I (IGF-1R) is insulin-like growth factor-I (IGF-1 receptor)

EGF is Epidermal growth factor

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 mls 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 4ºC	(Sigma, H3375)
1M	DTT	stored at -20ºC	(Sigma, D9779)
100mM	Na_3VO_4	stored at 4ºC	(Sigma, S6508)
1M	$MnCl_2$	stored at 4ºC	(Sigma, M3634)
1mM	ATP	stored at -20ºC	(Sigma, A3377)
Neat	Triton X-100	stored at room temperature	(Sigma, T9284)
10mg/ml	BSA	stored at 4ºC	(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 -20ºC

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 4ºC. 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.

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:

a.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 –20ºC

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

a.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 platewas 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 (ie. 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 (ie. 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.

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.

a.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
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

a.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 37ºC. 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 37ºC. The medium was removed (by pipetting) and then 100µl of 2x Laemmli buffer was added. The plates were stored at 4ºC 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 -20ºC 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

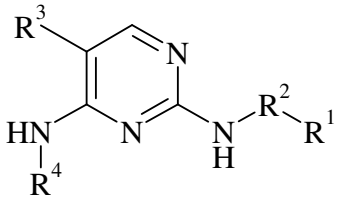
Cell samples were made up with 4x sample buffer, syringed with a 21 gauge needle and boiled for 5 minutes. Samples were loaded at equal volumes and a molecular weight ladder on 4-12% Bis-Tris gels (Invitrogen BV, The Netherlands) and the gels were run in an Xcell *SureLock*™ Mini-Cell apparatus (Invitrogen) 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 4ºC. 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.

Claims

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



(I)

wherein

R^1 represents a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring being optionally substituted by at least one substituent selected from C_1-C_6alkyl, C_1-C_6alkoxy (each of which may be optionally substituted by at least one substituent selected from halogen, amino, hydroxyl and trifluoromethyl), halogen, nitro, cyano, -NR^5R^6, carboxyl, hydroxyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, C_1-C_6alkoxycarbonyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylcarbonylamino, phenylcarbonyl, -$S(O)_m$$C_1$-$C_6$alkyl, -$C(O)NR^7R^8$, -$SO_2NR^{7a}R^{8a}$, and an unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring itself being optionally substituted by at least one substituent selected from C_1-C_6alkyl, C_1-C_6alkoxy (each of which may be optionally substituted by at least one substituent selected from halogen, amino, hydroxyl and trifluoromethyl), halogen, nitro, cyano, -NR^9R^{10}, carboxyl, hydroxyl, C_2-C_6alkenyl, C_3-C_6cycloalkyl, C_1-C_6alkoxycarbonyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylcarbonylamino, phenylcarbonyl, -$S(O)_n$$C_1$-$C_6$alkyl, -$C(O)NR^{11}R^{12}$ and -$SO_2NR^{11a}R^{12a}$;

m is 0, 1 or 2;

n is 0, 1 or 2;

R^2 represents a C_1-C_4alkyl group optionally substituted by at least one substituent selected from halogen, hydroxyl and C_1-C_3alkoxy;

R^3 represents hydrogen, halogen or trifluoromethyl;

R^4 represents a 5-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring being optionally substituted by at least one substituent selected from C_1-C_6alkyl, C_1-C_6alkoxy (each of which may be optionally substituted by at least one substituent selected from halogen, amino, hydroxyl and trifluoromethyl), halogen, nitro, cyano, -$NR^{13}R^{14}$, carboxyl, hydroxyl, C_2-C_6alkenyl,

C_3-C_6cycloalkyl, C_1-C_4alkoxycarbonyl, C_1-C_4alkylcarbonyl, C_1-C_4alkylcarbonylamino, phenylcarbonyl, -$S(O)_pC_1$-C_4alkyl, -$C(O)NR^{15}R^{16}$ and -$SO_2NR^{15a}R^{16a}$;

p is 0, 1 or 2;

R^5 and **R^6** each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^5 and R^6 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^7 and **R^8** each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^7 and R^8 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{7a} and **R^{8a}** each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{7a} and R^{8a} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^9 and **R^{10}** each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{11} and **R^{12}** each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{11a} and **R^{12a}** each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{11a} and R^{12a} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{13} and **R^{14}** each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{13} and R^{14} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

R^{15} and **R^{16}** each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{15} and R^{16} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle; and

R^{15a} and **R^{16a}** each independently represent hydrogen, C_1-C_4alkyl or C_3-C_6cycloalkyl, or R^{15a} and R^{16a} together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1, wherein, R^1 represents a 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring being optionally substituted by at least one substituent selected from C_1-C_6alkyl, C_1-C_6alkoxy (each of which may be optionally substituted by at least one substituent selected from hydroxyl), halogen, -C(O)NR^7R^8, C_1-C_6alkoxycarbonyl, and an unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom selected from nitrogen and oxygen, the ring itself being optionally substituted by at least one substituent selected from C_1-C_6alkyl, C_1-C_6alkoxy (each of which may be optionally substituted by at least one substituent selected from halogen), halogen and cyano; wherein R^7 and R^8 are both hydrogen or R^7 and R^8 together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle; or a pharmaceutically acceptable salt or solvate thereof.

3. A compound according to claim 1 or claim 2, R^1 represents pyridyl, imidazolyl, isoxazolyl, pyrazolyl, furyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl or thienyl; said pyridyl, imidazolyl, isoxazolyl, pyrazolyl, furyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl and thienyl being optionally substituted by at least one substituent selected from methyl, isopropyl, hydroxymethyl, methoxy, chloro, bromo, carbamoyl, methoxycarbonyl, pyrrolidin-1-ylcarbonyl, phenyl and pyridyl; said phenyl or pyridyl being optionally substituted by at least one substituent selected from methyl, trifluoromethyl, methoxy, ethoxy, trifluoromethoxy, fluoro, chloro, bromo and cyano; or a pharmaceutically acceptable salt or solvate thereof.

4. A compound according to any one of claims 1 to 3, wherein R^2 represents a C_1-C_4alkyl group; or a pharmaceutically acceptable salt or solvate thereof.

5. A compound according to any one of claims 1 to 4, wherein R^3 represents hydrogen or halogen; or a pharmaceutically acceptable salt or solvate thereof.

6. A compound according to any one of claims 1 to 5, wherein, R^4 represents a 5-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, the ring being optionally substituted by at least one substituent selected from C_1-C_6alkyl and C_3-C_6cycloalkyl; or a pharmaceutically acceptable salt or solvate thereof.

7. A compound according to claim 6, wherein, in R^4, the 5-membered heteroaromatic ring is pyrazolyl, the ring being optionally substituted by at least one substituent selected from methyl, ethyl, isopropyl, propyl, *t*-butyl and cyclopropyl; or a pharmaceutically acceptable salt or solvate thereof.

8. A compound according to claim 1, wherein

R^1 represents pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 2-methoxypyrid-5-yl, 2-cyanopyrid-5-yl, 3-bromopyrid-5-yl, 3-(pyrid-2-yl)pyrid-5-yl, 4-(pyrid-2-yl)pyrid-2-yl, 3-chloropyrid-2-yl, 3-methylpyrid-2-yl, 6-methylpyrid-2-yl, 5,6-dimethylpyrid-2-yl, imidazol-4-yl, imidazol-5-yl, 3-methylisoxazol-5-yl, 5-methylisoxazol-3-yl, 3-isopropylisoxazol-5-yl, 3-methoxycarbonylisoxazol-5-yl, 3-(hydroxymethyl)isoxazol-5-yl, 3-carbamoylisoxazol-5-yl, 3-(pyrrolidin-1-ylcarbonyl)isoxazol-5-yl, 3-phenylisoxazol-5-yl, 3-(pyrid-2-yl)isoxazol-5-yl, 3-(2-methoxypyrid-3-yl)isoxazol-5-yl, 3-(2-methoxyphenyl)isoxazol-5-yl, 3-(3-methoxyphenyl)isoxazol-5-yl, 3-(2-ethoxyphenyl)isoxazol-5-yl, 3-(2-trifluoromethylphenyl)isoxazol-5-yl, 3-(2-trifluoromethoxyphenyl)isoxazol-5-yl, 3-(2-chlorophenyl)isoxazol-5-yl, 3-(2-bromophenyl)isoxazol-5-yl, 3-(2-methylphenyl)isoxazol-5-yl, 3-(2-fluorophenyl)isoxazol-5-yl, 3-(2-cyanophenyl)isoxazol-5-yl, 5-methylpyrazol-4-yl, fur-2-yl, fur-3-yl, 5-methylfur-2-yl, pyrazin-2-yl, 2-methylpyrazin-5-yl, pyridazin-3-yl, pyrimidin-4-yl, 1-methylpyrrol-2-yl and thien-3-yl;

R^2 represents methyl, ethyl and propyl;

R^3 represents hydrogen, chloro or bromo; and

R^4 represents 5-methylpyrazol-3-yl, 5-ethylpyrazol-3-yl, 5-isopropylpyrazol-3-yl, 5-propylpyrazol-3-yl, 5-*t*-butylpyrazol-3-yl and 5-cyclopropylpyrazol-3-yl;

or a pharmaceutically acceptable salt or solvate thereof.

9. A compound selected from:

5-Bromo-2-(3-methylisoxazol-5-ylmethylamino)-4-(5-cyclopropyl-1H-pyrazol-3-ylamino)pyrimidine,

5-Chloro-2-(3-phenylisoxazol-5-ylmethylamino)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidine,

5-Chloro-2-(3-pyrid-2-ylisoxazol-5-ylmethylamino)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidine,

5-Bromo-2-(3-pyrid-2-ylisoxazol-5-ylmethylamino)-4-(5-methyl-1H-pyrazol-3-ylamino)pyrimidine,

5-Chloro-2-(3-methylisoxazol-5-ylmethylamino)-4-(5-*tert*-butyl-1H-pyrazol-3-ylamino)pyrimidine,

5-Bromo-2-(3-methylisoxazol-5-ylmethylamino)-4-(5-ethyl-1H-pyrazol-3-ylamino)pyrimidine,

5-Chloro-2-[3-(2-fluorophenyl)isoxazol-5-ylmethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Bromo-2-[3-(2-fluorophenyl)isoxazol-5-ylmethylamino]-4-(5-methyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Chloro-2-[3-(2-fluorophenyl)isoxazol-5-ylmethylamino]-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Bromo-4-(5-isopropyl-1*H*-pyrazol-3-ylamino)-2-(pyrid-2-ylmethylamino) pyrimidine,

5-Bromo-2-(3-methylisoxazol-5-ylmethylamino)-4-(5-propyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Bromo-2-(3-methylisoxazol-5-ylmethylamino)-4-(5-isopropyl-1*H*-pyrazol-3-ylamino)pyrimidine,

5-Chloro-2-[3-(pyrid-2-yl)isoxazol-5-ylmethylamino]-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine,

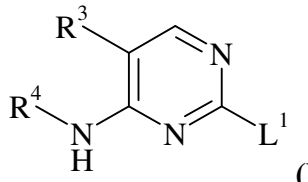
5-Bromo-2-[3-(pyrid-2-yl)isoxazol-5-ylmethylamino]-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine, and

5-Bromo-2-(3-bromopyrid-5-ylmethylamino)-4-(5-*tert*-butyl-1*H*-pyrazol-3-ylamino)pyrimidine,

and pharmaceutically acceptable salts and solvates of any one thereof.

10. A process for the preparation of a compound according to claim 1, which comprises:

(i) reacting a compound of formula

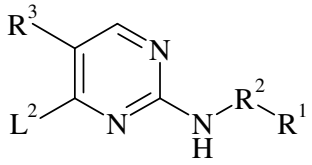


(II)

wherein L^1 represents a leaving group and R^3 and R^4 are as defined in formula **(I)**, with a

compound of formula **(III)**, H_2N-R^2-R^1, wherein R^1 and R^2 are as defined in formula **(I)**; or

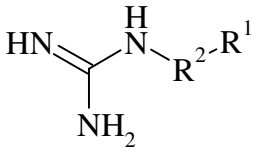
(ii) reacting a compound of formula



(IV)

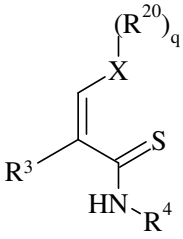
wherein L^2 represents a leaving group and R^1, R^2 and R^3 are as defined in formula **(I)**, with a compound of formula **(V)**, H_2N-R^4, wherein R^4 is as defined in formula **(I)**; or

(iii) reacting a compound of formula



(VI)

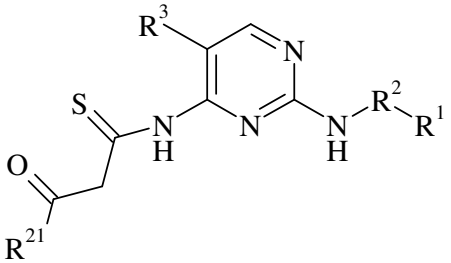
wherein R^1 and R^2 are as defined in formula **(I)**, with a compound of formula



(VII)

wherein X represents an oxygen atom and q is 1 or X represents a nitrogen atom and q is 2, each R^{20} independently represents a C_1-C_6alkyl group and R^3 and R^4 are as defined in formula **(I)**; or

(iv) when R^4 represents a substituted pyrazolyl, reacting a compound of formula



(VIII)

wherein R^{21} represents a C_1-C_6alkyl or C_3-C_6cycloalkyl group and R^1, R^2 and R^3 are as defined in formula **(I)** with hydrazine;

and optionally after (i), (ii), (iii) or (iv) carrying out one or more of the following:

- converting the compound obtained to a further compound according to claim 1
- forming a pharmaceutically acceptable salt or solvate of the compound.

11. A pharmaceutical composition comprising a compound of formula **(I)**, or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

12. A process for the preparation of a pharmaceutical composition as claimed in claim 11 which comprises mixing a compound of formula **(I)**, or a pharmaceutically acceptable salt or solvate thereof, as defined in any one of claims 1 to 9 with a pharmaceutically acceptable adjuvant, diluent or carrier.

13. A compound of formula **(I)**, or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 for use in therapy.

14. Use of a compound of formula **(I)**, or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 in the manufacture of a medicament for use in the treatment of cancer.

15. Use of a compound of formula **(I)**, or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9 in the manufacture of a medicament for use in modulating insulin-like growth factor-1 receptor activity.

16. A method of treating cancer which comprises administering to a patient a therapeutically effective amount of a compound of formula **(I)**, or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9.

17. A method of modulating insulin-like growth factor-1 receptor activity which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula **(I)**, or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 9.

18. A compound according to claim 1, wherein, in R^1, the 5- or 6-membered heteroaromatic ring is selected from thienyl, pyrazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, triazolyl, tetrazolyl, imidazolyl, pyrazinyl, pyridazinyl, pyrimidinyl and pyridyl; or a pharmaceutically acceptable salt or solvate thereof.

19. A compound according to claim 1, wherein, in R^1, the 5- or 6-membered heteroaromatic ring is selected from thienyl, pyrazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, triazolyl, tetrazolyl, imidazolyl, pyrazinyl and pyridyl; or a pharmaceutically acceptable salt or solvate thereof.

20. A compound according to claim 1, wherein, in R^1, the unsaturated 5- to 6-membered ring is selected from phenyl, cylopentenyl, cyclohexenyl, thienyl, pyrazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, triazolyl, tetrazolyl, imidazolyl, pyrazinyl, pyridazinyl, pyrimidinyl and pyridyl; or a pharmaceutically acceptable salt or solvate thereof.

21. A compound according to claim 1, wherein, in R^1, the unsaturated 5- to 6-membered ring is selected from phenyl, cylopentenyl, cyclohexenyl, thienyl, pyrazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, triazolyl, tetrazolyl, imidazolyl, pyrazinyl and pyridyl; or a pharmaceutically acceptable salt or solvate thereof.

22. A compound according to claim 1, wherein R^3 represents a halogen atom; or a pharmaceutically acceptable salt or solvate thereof.

23. A compound according to claim 1, wherein, in R^4, the 5-membered heteroaromatic ring is selected from thienyl, pyrazolyl, isoxazolyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, triazolyl, tetrazolyl and imidazolyl; or a pharmaceutically acceptable salt or solvate thereof.

24. A compound according to claim 1, wherein, in R^4, the 5-membered heteroaromatic ring is pyrazolyl; or a pharmaceutically acceptable salt or solvate thereof.