PYRIMIDINE DERIVATIVES

The present invention relates to novel pyrimidine derivatives, to pharmaceutical compositions containing these derivatives and to their use in therapy, in particular in the prevention and treatment of solid tumour disease in a warm blooded animal such as man.

Many of the current treatment regimes for cell proliferation diseases such as psoriasis and cancer utilise compounds which inhibit DNA synthesis. Such compounds are toxic to cells generally but their toxic effect on rapidly dividing cells such as tumour cells can be beneficial. Alternative approaches to target tumours using agents that act on mechanisms other than the inhibition of DNA synthesis have the potential to display enhanced selectivity of action.

In recent years it has been discovered that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene *i.e.* a gene which, on activation, leads to the formation of malignant tumour cells (Bradshaw, Mutagenesis, 1986, 1, 91). Several such oncogenes give rise to the production of peptides which are receptors for growth factors. Activation of the growth factor receptor complex subsequently leads to an increase in cell proliferation. It is known, for example, that several oncogenes encode tyrosine kinase enzymes and that certain growth factor receptors are also tyrosine kinase enzymes (Yarden *et al.*, Ann. Rev. Biochem., 1988, 57, 443; Larsen *et al.*, Ann. Reports in Med. Chem., 1989, Chpt. 13).

The first group of tyrosine kinases to be identified arose from such viral oncogenes, for example $pp60^{v\text{-}Src}$ tyrosine kinase (otherwise known as v-Src), and the corresponding tyrosine kinases in normal cells, for example $pp60^{c\text{-}Src}$ tyrosine kinase (otherwise known as c-Src).

Receptor tyrosine kinases are important in the transmission of biochemical signals which initiate a variety of cell responses including proliferation, survival and migration. They are large enzymes which span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor (EGF) and an intracellular portion which functions as a kinase to phosphorylate tyrosine amino acids in proteins and hence to influence cell proliferation. Various classes of receptor tyrosine kinases are known (Wilks, Advances in Cancer Research, 1993, 60 43-73) and are classified on the basis of the growth factor family to which they bind. This

classification includes Class I receptor tyrosine kinases comprising the EGF family of receptor tyrosine kinases such as the EGF, TGFα, Neu and erbB receptors, Class II receptor tyrosine kinases comprising the insulin family of receptor tyrosine kinases such as the insulin and IGF1 receptors and insulin-related receptor (IRR) and Class III receptor tyrosine kinases comprising the platelet-derived growth factor (PDGF) family of receptor tyrosine kinases such as the PDGFα, PDGFβ and colony-stimulating factor 1 (CSF1) receptors.

The Eph family is the largest known family of receptor tyrosine kinases, with 14 receptors and 8 cognate ephrin ligands identified in mammals (Reviewed in Kullander and Klein, Nature Reviews Molecular Cell Biology, 2002, 3, 475-486). The receptor family is further sub-divided into two sub-families, which are defined largely by the homology of the extracellular domains and their affinity towards a particular ligand type. In general, all Ephs contain an intracellular tyrosine kinase domain and an extracellular Ig-like domain with a cysteine-rich region with 19 conserved cysteines and two fibronectin type III domains. The A-class of Ephs consists of 8 receptors, termed EphA1-8, which generally bind to their cognate ephrinA class of ligands, termed ephrinA1-5. The B-class consists of 6 receptors, termed EphB1-6, which bind to their cognate ephrinB ligands, termed ephrinB1-3. Eph receptor ligands are unusual and different to most other receptor tyrosine kinase ligands in that they are also tethered to cells, via a glycosylphosphatidylinositol linker in ephrinA ligands or an integral transmembrane region in ephrinB ligands. Binding of ephrin ligand to the Eph partner induces a conformational change within the Eph intracellular domain that enables phosphorylation of tyrosine residues within an auto-inhibitory juxtamembrane region, which relieves this inhibition of catalytic site and enables additional phosphorylation to stabilise the active conformation and generate more docking sites for downstream signalling effectors.

Furthermore, evidence indicates that Eph/ephrin signalling can regulate other cell responses such as proliferation and survival.

There is growing evidence that Eph receptor signalling may contribute to tumourigenesis in a wide variety of human cancers, either on tumour cells directly or indirectly via modulation of vascularisation. For instance, many Eph receptors are over-expressed in various tumour types (Reviewed in Surawska *et al.*, Cytokine & Growth Factor Reviews, 2004, 15, 419-433, Nakamoto and Bergemann, Microscopy Res and

Technique, 2002, 59, 58-67); EphA2 and other EphA receptor levels are elevated in diverse tumours such as leukemias, breast, liver, lung, ovarian and prostate. Similarly expression of EphB receptors including EphB4 is up-regulated in tumours such as neuroblastomas, leukemias, breast, liver, lung and colon. Moreover, various *in vitro* and *in vivo* studies, particularly relating to EphA2 and EphB4, have indicated that over-expression of Eph receptors on cancer cells is able to confer tumourigenic phenotypes such as proliferation and invasion, consistent with the speculated role in oncogenesis.

For instance, inhibition of EphB4 expression using interfering-RNA or antisense oligodeoxynucleotides inhibited proliferation, survival and invasion of PC3 prostate cancer cells *in vitro* and *in vivo* xenograft model (Xia *et al.*, Cancer Res., 2005, 65, 4623-4632). EphA2 over-expression in MCF-10A mammary epithelial cells is sufficient to cause tumourigenesis (Zelinski *et al.*, Cancer Res., 2001, 61, 2301-2306). Inhibition of EphA2 function with therapeutic antibodies (Coffman *et al.*, Cancer Res., 2003, 63, 7907-7912) or interfering-RNA (Landen *et al.*, Cancer Res., 2005, 15, 6910-6918) has been demonstrated to inhibit tumour growth in *in vivo* xenograft models. Expression of kinase-dead EphA2 mutant receptors in breast cancer cell lines inhibited growth and metastasis of xenograft tumours *in vivo*, consistent with an essential role of the kinase domain (Fang *et al.*, Oncogene, 2005, 24, 7859-7868).

In addition to compelling role of Eph receptors on tumour cells, there is good evidence that both EphA2 and EphB4 may contribute to tumour vascularisation (Reviewed in Brantley-Sieders *et al.*, Current Pharmaceutical Design, 2004, 10, 3431-3442, Cheng *et al.*, Cytokine and Growth Factor Reviews, 2002, 13, 75-85). Members of Eph family including both EphA2 and EphB4 are expressed on endothelial cells. Transgenic studies have shown that disruption of EphB4 (Gerety *et al.*, Molecular Cell, 1999, 4, 403-414) or its ligand ephrinB2 (Wang *et al.*, Cell, 1998, 93, 741-753) causes embryonic lethality associated with vascular modelling defects consistent with a critical role in vessel development. EphB4 activation stimulates endothelial cell proliferation and migration *in vitro* (Steinle *et al.*, J. Biol. Chem., 2002, 277, 43830-43835).

Moreover, inhibition of EphB4 signalling using soluble extracellular-domains of EphB4 have been shown to inhibit tumour growth and angiogenesis in *in vivo* xenograft studies (Martiny-Baron et al., Neoplasia, 2004, 6, 248-257, Kertesz *et al.*, Blood, 2005, Pre-published online). Similarly, soluble EphA2 inhibited tumour vascularisation in a

variety of *in vivo* models (Brantley *et al.*, Oncogene, 2002, 21, 7011-7026, Cheng *et al.*, Neoplasia, 2003, 5, 445-456).

Accordingly it has been recognised that an inhibitor of Eph receptors, particularly EphB4 or EphA2, should be of value as a selective inhibitor of the proliferation and survival of tumour cells by either targeting tumour cells directly or via effects on tumour vascularisation. Thus, such inhibitors should be valuable therapeutic agents for the containment and/or treatment of tumour disease.

It is also known that certain tyrosine kinases belong to the class of non-receptor tyrosine kinases which are located intracellularly and are involved in the transmission of biochemical signals such as those that influence tumour cell motility, dissemination and invasiveness and subsequently metastatic tumour growth (Ullrich *et al.*, Cell, 1990, 61, 203-212, Bolen *et al.*, FASEB J., 1992, 6, 3403-3409, Brickell *et al.*, Critical Reviews in Oncogenesis, 1992, 3, 401-406, Bohlen *et al.*, Oncogene, 1993, 8, 2025-2031, Courtneidge *et* al., Semin. Cancer Biol., 1994, 5, 239-246, Lauffenburger *et al.*, Cell, 1996, 84, 359-369, Hanks *et al.*, BioEssays, 1996, 19, 137-145, Parsons *et al.*, Current Opinion in Cell Biology, 1997, 9, 187-192, Brown *et al.*, Biochimica et Biophysica Acta, 1996, 1287, 121-149 and Schlaepfer *et al.*, Progress in Biophysics and Molecular Biology, 1999, 71, 435-478). Various classes of non-receptor tyrosine kinases are known including the Src family such as the Src, Lyn and Yes tyrosine kinases, the Abl family such as Abl and Arg and the Jak family such as Jak 1 and Tyk 2.

It is known that the Src family of non-receptor tyrosine kinases are highly regulated in normal cells and in the absence of extracellular stimuli are maintained in an inactive conformation. However, some Src family members, for example c-Src tyrosine kinase, are frequently significantly activated (when compared to normal cell levels) in common human cancers such as gastrointestinal cancer, for example colon, rectal and stomach cancer (Cartwright *et al.*, Proc. Natl. Acad. Sci. USA, 1990, 87, 558-562 and Mao *et al.*, Oncogene, 1997, 15, 3083-3090), and breast cancer (Muthuswamy *et al.*, Oncogene, 1995, 11, 1801-1810). The Src family of non-receptor tyrosine kinases has also been located in other common human cancers such as non-small cell lung cancers (NSCLCs) including adenocarcinomas and squamous cell cancer of the lung (Mazurenko *et* al., European Journal of Cancer, 1992, 28, 372-7), bladder cancer (Fanning *et al.*, Cancer

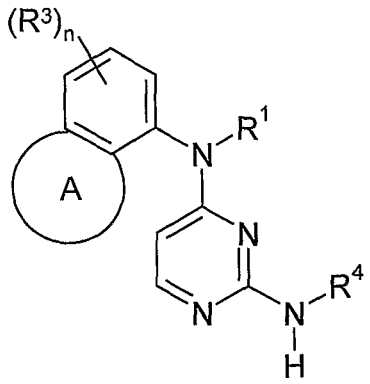
Research, 1992, 52, 1457-62), oesophageal cancer (Jankowski *et al.*, Gut, 1992, 33, 1033-8), cancer of the prostate, ovarian cancer (Wiener *et al.*, Clin. Cancer Research, 1999, 5, 2164-70) and pancreatic cancer (Lutz *et at.*, Biochem. and Biophys. Res. Comm., 1998, 243, 503-8). As further human tumour tissues are tested for the Src family of non-receptor tyrosine kinases it is expected that its widespread prevalence will be established.

It is further known that the predominant role of c-Src non-receptor tyrosine kinase is to regulate the assembly of focal adhesion complexes through interaction with a number of cytoplasmic proteins including, for example, focal adhesion kinase and paxillin. In addition c-Src is coupled to signalling pathways that regulate the actin cytoskeleton which facilitates cell motility. Likewise, important roles are played by the c-Src, c-Yes and c-Fyn non-receptor tyrosine kinases in integrin mediated signalling and in disrupting cadherin-dependent cell-cell junctions (Owens *et* al., Molecular Biology of the Cell, 2000, 11, 51-64 and Klinghoffer *et al.*, EMBO Journal, 1999, 18, 2459-2471). Cellular motility is necessarily required for a localised tumour to progress through the stages of dissemination into the blood stream, invasion of other tissues and initiation of metastatic tumour growth. For example, colon tumour progression from localised to disseminated, invasive metastatic disease has been correlated with c-Src non-receptor tyrosine kinase activity (Brunton *et al.*, Oncogene, 1997, 14, 283-293, Fincham *et al.*, EMBO J, 1998, 17, 81-92 and Verbeek *et al.*, Exp. Cell Research, 1999, 248, 531-537).

Accordingly it has been recognised that an inhibitor of such non-receptor tyrosine kinases should be of value as a selective inhibitor of the motility of tumour cells and as a selective inhibitor of the dissemination and invasiveness of mammalian cancer cells leading to inhibition of metastatic tumour growth. In particular an inhibitor of such non-receptor tyrosine kinases should be of value as an anti-invasive agent for use in the containment and/or treatment of solid tumour disease.

The applicants have found that certain pyrimidines are useful in the inhibition of EphB4 and, in some cases, EphA2 and Src kinase as well. Such pyrimidines are therefore are useful in therapy, where such enzymes are implicated.

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



(I)

where **R**[1] is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, or C_{2-6}alkynyl, wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by one or more substituents selected from cyano, nitro, $-OR^2$, $-NR^{2a}R^{2b}$, $-C(O)NR^{2a}R^{2b}$, $-N(R^{2a})C(O)R^2$, halo or haloC_{1-4}alkyl (such as trifluoromethyl), where R^2, R^{2a} and R^{2b} are selected from hydrogen or C_{1-6}alkyl such as methyl, or R^{2a} and R^{2b} together with the nitrogen atom to which they are attached may form a 5 or 6-membered heterocyclic ring, which optionally contains an additional heteroatom selected from N, O or S;

ring **A** is fused 5 or 6-membered carbocyclic or heterocyclic ring, which is saturated or unsaturated, and is optionally substituted on any available carbon atom by one or more substituent groups selected from halo, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, $-S(O)_z-C_{1-6}$alkyl (where z is 0, 1 or 2), or $-NR^aR^b$ (where R^a and R^b are each independently selected from hydrogen, C_{1-4}alkyl, or C_{1-4}alkylcarbonyl), and where any nitrogen atoms in the ring are optionally substituted by a C_{1-6}alkyl or C_{1-6}alkylcarbonyl;
n is 0, 1, 2 or 3

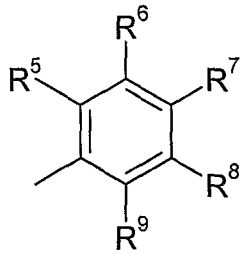
and each group **R**[3] is independently selected from halo, trifluoromethyl, cyano, nitro or a group of sub-formula (i) :

$$-X^1-R^{11} \qquad (i)$$

where **X**[1] is selected from a direct bond or O, S, SO, SO_2, OSO_2, NR^{13}, CO, $CH(OR^{13})$, $CONR^{13}$, $N(R^{13})CO$, $SO_2N(R^{13})$, $N(R^{13})SO_2$, $C(R^{13})_2O$, $C(R^{13})_2S$, $C(R^{13})_2N(R^{13})$ and $N(R^{13})C(R^{13})_2$, wherein **R**[13] is hydrogen or C_{1-6}alkyl and **R**[11] is selected from hydrogen, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}cycloalkyl, aryl or heterocyclyl, C_{3-8}cycloalkylC_{1-6}

alkyl, arylC_{1-6} alkyl or heterocyclylC_{1-6} alkyl, any of which may be optionally substituted with one or more groups selected from halo, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, C_{1-6}alkoxy, C_{2-6}alkenyoxyl, C_{2-6}alkynyloxy, C_{1-6}alkylthio, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, C_{1-6}alkylamino, di-(C_{1-6}alkyl)amino, C_{1-6}alkoxycarbonyl, N-C_{1-6}alkylcarbamoyl, N, N-di-(C_{1-6}alkyl)carbamoyl, C_{2-6}alkanoyl, C_{2-6}alkanoyloxy, C_{2-6}alkanoylamino, N-C_{1-6}alkyl-C_{2-6}alkanoylamino, C_{3-6}alkenoylamino, N-C_{1-6}alkyl-C_{3-6}alkenoylamino, C_{3-6}alkynoylamino, N-C_{1-6}alkyl- C_{3-6}alkynoylamino, N-C_{1-6}alkylsulphamoyl, N,N-di-(C_{1-6}alkyl)sulphamoyl, C_{1-6}alkanesulphonylamino and N-C_{1-6}alkyl-C_{1-6}alkanesulphonylamino, and any heterocyclyl group within R^{11} optionally bears 1 or 2 oxo or thioxo substituents; and

$\mathbf{R^4}$ is a group of sub-formula (iii)



(iii)

where $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$ and $\mathbf{R^9}$ are each independently selected from:

(a) hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl), heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) and wherein any aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl), heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) groups are optionally substituted on any available carbon atoms by halo, hydroxy, cyano, amino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino, and any nitrogen atoms present in a heterocyclyl group may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl, and where any sulphur atoms may be optionally oxidised to a sulphur oxide;

(b) a group of sub-formula (iv):

$$-X^2-R^{14} \qquad \text{(iv)}$$

where **X^2** is selected from O, NR^{16}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{16})$, $CON(R^{16})$, $N(R^{16})CO$, $-N(R^{16})C(O)N(R^{16})-$, $-N(R^{16})C(O)O-$, $SON(R^{16})$, $N(R^{16})SO$, $SO_2N(R^{16})$, $N(R^{16})SO_2$, $C(R^{16})_2O$, $C(R^{16})_2S$ and $N(R^{16})C(R^{16})_2$, where each R^{16} is independently selected from hydrogen or C_{1-6}alkyl,

R^{14} is hydrogen, C_{1-6} alkyl, trifluoromethyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, or a 4- to 8-membered mono or bicyclic heterocyclyl ring (including 5 or 6 membered heteroaryl rings) or 4- to 8-membered mono or bicyclic heterocyclyl-C_{1-6}alkyl groups (including 5 or 6 membered heteroaryl-C_{1-6}alkyl groups) and wherein any aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl), heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) groups are optionally substituted on any available carbon atoms by oxo, halo, cyano, amino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino and any nitrogen atoms present in the heterocyclyl moieties may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl, and where any sulphur atoms may be optionally oxidised to a sulphur oxide;

(c) a group of sub-formula (v):

$$-X^3-R^{15}-Z \qquad \text{(v)}$$

where **X^3** is a direct bond or is selected from O, NR^{17}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{17})$, $CON(R^{17})$, $N(R^{17})CO$, $-N(R^{17})C(O)N(R^{17})-$, $-N(R^{17})C(O)O-$, $SO_2N(R^{17})$, $N(R^{17})SO_2$, $C(R^{17})_2O$, $C(R^{17})_2S$ and $N(R^{17})C(R^{17})_2$, where each R^{17} is independently selected from hydrogen or C_{1-6}alkyl;

R^{15} is a C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene, arylene, C_{3-12} carbocyclyl, heterocyclyl (including heteroaryl), any of which may be optionally substituted by one or more groups selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, amino, C_{1-6}alkylamino or di-(C_{1-6}alkyl)amino;

Z is halo, trifluoromethyl, cyano, nitro, aryl, C_{3-12} carbocyclyl or heterocyclyl (including heteroaryl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl and

C_{1-6}alkoxy and wherein any heterocyclyl group within Z optionally bears 1 or 2 oxo substituents,

or Z is a group of sub-formula (vi)

$$-X^4-R^{18} \qquad \text{(vi)}$$

where $\mathbf{X^4}$ is selected from O, NR^{19}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{19})$, $CON(R^{19})$, $N(R^{19})CO$, $SO_2N(R^{19})$, $-N(R^{19})C(O)N(R^{19})-$, $-N(R^{19})C(O)O-$ $N(R^{19})SO_2$, $C(R^{19})_2O$, $C(R^{19})_2S$ and $N(R^{19})C(R^{19})_2$, where each R^{19} is independently selected from hydrogen or C_{1-6}alkyl; and R^{18} is selected from hydrogen, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl) or heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl and C_{1-6}alkoxy, and wherein any heterocyclyl group within R^{18} optionally bears 1 or 2 oxo substituents;

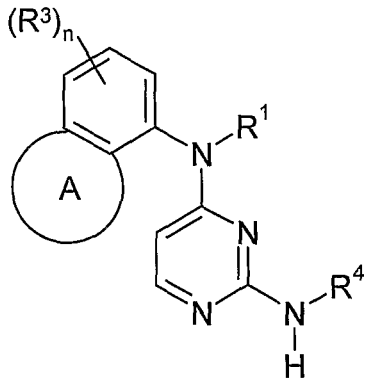
or

(d) R^5 and R^6, R^6 and R^7, R^7 and R^8 or R^8 and R^9 are joined together to form a fused 5, 6 or 7-membered ring, wherein said ring is unsaturated or partially or fully saturated and is optionally substituted on any available carbon atom by halo, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, amino, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino, and said ring may contain one or more heteroatoms selected from oxygen, sulphur or nitrogen, where sulphur atoms may be optionally oxidised to a sulphur oxide, where any CH_2 groups may be substituted by a C(O) group, and where nitrogen atoms, depending upon valency considerations, may be substituted by a group R^{21}, where R^{21} is selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl;

or a pharmaceutically acceptable salt thereof,

with the proviso that if Ring A, together with the phenyl ring to which it is attached, forms an indazol-4-yl group, then R^1 is not hydrogen.

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



(I)

where $\mathbf{R^1}$ is selected from hydrogen or optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl or optionally substituted C_{2-6}alkynyl;

ring **A** is fused 5 or 6-membered carbocyclic or heterocyclic ring which is optionally substituted on a carbon atom by one or more halo groups or C_{1-6}alkyl groups, and where any nitrogen atoms in the ring are optionally substituted by a C_{1-6}alkyl or C-$_{1-6}$alkylcarbonyl;

n is 0, 1, 2 or 3

and each group $\mathbf{R^3}$ is independently selected from halo, trifluoromethyl, cyano, nitro or a group of sub-formula (i) :

$$-X^1-R^{11} \qquad (i)$$

where $\mathbf{X^1}$ is selected from a direct bond or O, S, SO, SO_2, OSO_2, NR^{13}, CO, $CH(OR^{13})$, $CONR^{13}$, $N(R^{13})CO$, $SO_2N(R^{13})$, $N(R^{13})SO_2$, $C(R^{13})_2O$, $C(R^{13})_2S$, $C(R^{13})_2N(R^{13})$ and $N(R^{13})C(R^{13})_2$, wherein $\mathbf{R^{13}}$ is hydrogen or C_{1-6}alkyl and

$\mathbf{R^{11}}$ is selected from hydrogen, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}cycloalkyl, aryl or heterocyclyl, C_{1-6} alkylC_{3-8}cycloalkyl, C_{1-6} alkylaryl or C_{1-6} alkylheterocyclyl,, any of which may be optionally substituted with one or more groups selected from halo, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, C_{1-6}alkoxy, C_{2-6}alkenyoxyl, C_{2-6}alkynyloxy, C_{1-6}alkylthio, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, C_{1-6}alkylamino, di-(C_{1-6}alkyl)amino, C_{1-6}alkoxycarbonyl, N-C_{1-6}alkylcarbamoyl, N, N-di-(C_{1-6}alkyl)carbamoyl, C_{2-6}alkanoyl, C_{2-6}alkanoyloxy, C_{2-6}alkanoylamino, N-C_{1-6}alkyl-

C_{2-6}alkanoylamino, C_{3-6}alkenoylamino, N-C_{1-6}alkyl-C_{3-6}alkenoylamino, C_{3-6}alkynoylamino, N-C_{1-6}alkyl- C_{3-6}alkynoylamino, N-C_{1-6}alkylsulphamoyl, N,N-di-(C_{1-6}alkyl)sulphamoyl, C_{1-6}alkanesulphonylamino and N-C_{1-6}alkyl-C_{1-6}alkanesulphonylamino, and any heterocyclyl group within R^{11} optionally bears 1 or 2 oxo or thioxo substituents; and

R^4 is an optionally substituted phenyl ring, wherein one or more adjacent substituents may be joined together to form a fused bicyclic or tricyclic ring; or a pharmaceutically acceptable salt thereof.

It is to be understood that, insofar as certain of the compounds of Formula (I) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

It is to be understood that certain compounds of Formula (I) defined above may exhibit the phenomenon of tautomerism. In particular, tautomerism may affect any heterocyclic groups that bear 1 or 2 oxo substituents. It is also to be understood that the present invention includes in its definition any such tautomeric form, or a mixture thereof, which possesses the above-mentioned activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings or named in the Examples.

It is to be understood that certain compounds of Formula I above may exist in unsolvated forms as well as solvated forms, such as, for example, hydrated forms. It is also to be understood that the present invention encompasses all such solvated forms that possess anticancer or antitumour activity.

It is also to be understood that certain compounds of the Formula I may exhibit polymorphism, and that the present invention encompasses all such forms which possess anticancer or antitumour activity.

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

groups. In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and tert-butyl. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only, references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only. An analogous convention applies to other generic terms, for example (1-6C)alkoxy includes methoxy, ethoxy and isopropoxy, (1-6C)alkylamino includes methylamino, isopropylamino and ethylamino, and di-[(1-6Calkyl]amino includes dimethylamino, diethylamino and N-methyl-N-isopropylamino. Similarly alkenyl or alkynyl groups may be straight chain or branched.

The term "aryl" refers to phenyl or naphthyl, particularly phenyl.

The terms "halo" or "halogen" refers to fluoro, chloro, bromo, or iodo.

The term "heterocyclyl" or "heterocyclic ring", unless otherwise defined herein, refers to saturated, partially saturated or unsaturated, mono, bicyclic or tricyclic rings containing 3-15 atoms, of which at least one atom is chosen from nitrogen, sulphur or oxygen. These groups may, unless otherwise specified, be carbon or nitrogen linked. In addition, or a ring sulphur atom may be optionally oxidised to form the S-oxides. More particularly, a "heterocyclyl" or "heterocyclic ring" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 3-12 atoms, and especially 4 to 10 atoms, of which at least one atom is chosen from nitrogen, sulphur or oxygen. Monocyclic "heterocyclyls" or "heterocyclic rings" suitably contain from 3-7 ring atoms, in particular 5 or 6 ring atoms.

Examples and suitable values of the term "heterocyclyl" are thienyl, piperidinyl, morpholinyl, furyl, thiazolyl, pyridyl, imidazolyl, 1,2,4-triazolyl, thiomorpholinyl, coumarinyl, pyrimidinyl, phthalidyl, pyrazolyl, pyrazinyl, pyridazinyl, benzothienyl, benzimidazolyl, tetrahydrofuryl, [1,2,4]triazolo[4,3-a]pyrimidinyl, piperidinyl, indolyl, indazolyl, benzothiazolyl, benzoxazolyl, 1,3-benzodioxolyl, pyrrolidinyl, pyrrolyl, quinolinyl, isoquinolinyl, isoxazolyl, benzofuranyl, 1,2,3-thiadiazolyl, 1,2,5-thiadiazolyl, pyrimidinyl, 2,1-benzisoxazolyl, 4,5,6,7-tetrahydro-2*H*-indazolyl, imidazo[2,1-*b*][1,3]thiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholinyl, 2,3-dihydro-1-benzofuryl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzothiazolyl, 3,4-dihydro-2H-benzodioxepinyl, 2,3-dihydro-1,4-benzodioxinyl, chromanyl, 2,3-dihydrobenzofuranyl, imidazo[2,1-b][1,3]thiazolyl, isoindolinyl, oxazolyl,

pyridazinyl, quinoxalinyl, tetrahydrofuryl, 4,5,6,7-tetrahydro-1-benzofuryl, 4,5,6,7-tetrahydro-2H-indazolyl, 4,5,6,7-tetrahydro-1H-indolyl, tetrahydropyranyl or 1,2,3,4-tetrahydroquinolinyl.

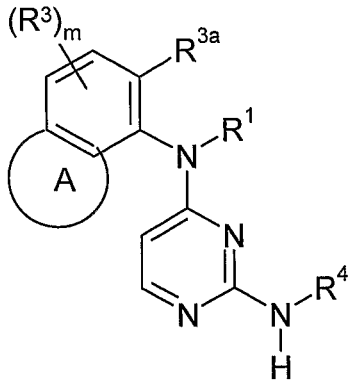
Heterocyclyl groups may be non-aromatic or aromatic in nature. Aromatic heterocyclyl groups are specifically referred to as heteroaryl. Heteroaryl groups are totally unsaturated, mono or bicyclic rings containing 3-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Suitably "heteroaryl" refers to a totally unsaturated, monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 8 - 10 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Examples and suitable values of the term "heteroaryl" are thienyl, furyl, thiazolyl, pyrazolyl, isoxazolyl, imidazolyl, pyrrolyl, thiadiazolyl, isothiazolyl, triazolyl, pyranyl, indolyl, pyrimidyl, pyrazinyl, pyridazinyl, benzothienyl, pyridyl and quinolyl.

As stated above, when R^1 is an optionally substituted C_{1-6}alkyl, optionally substituted C_{2-6}alkenyl or optionally substituted C_{2-6}alkynyl, optional substituents are suitably selected from cyano, $-OR^2$, $-NR^{2a}R^{2b}$, $-C(O)NR^{2a}R^{2b}$, or $-N(R^{2a})C(O)R^2$, halo or haloC_{1-4}alkyl such as trifluoromethyl, where R^2, R^{2a} and R^{2b} are selected from hydrogen or C_{1-6}alkyl such as methyl, or R^{2a} and R^{2b} together with the nitrogen atom to which they are attached may form a heterocyclic ring which optionally contains an additional heteroatom.

In one embodiment of the invention, R^1 is hydrogen.

In a further embodiment, n is 0, 1, or 2. For instance, n is 0 or 1. In yet a further embodiment, n is 1.

Where n is 1 or more, a substituent R^3 is suitably positioned on the available ortho-carbon atom of the ring, forming a compound of formula (IA)



(IA)

where A, R^1, R^3 and R^4 are as defined herein relation to formula (I), R^{3a} is a group R^3 as defined herein, and in particular is halo, and m is 0, 1 or 2. Particular examples of A groups are set out below, and include for example groups A' as defined below. In particular A is $-OCH_2O-$, $O-CF_2-O-$, -OCH=N-, -N=CH-O-, -S-CH=N-, -N=CH-S-, -NH-N=CH-, or -CH=N-NH-.

When n is other than zero, particular examples of R^3 or R^{3a} groups are groups selected from halo, trifluoromethyl, cyano, hydroxy, C_{1-6}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl and C_{1-6}alkoxy.

For instance, R^3 or R^{3a} may be selected from chloro, fluoro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, ethynyl, methoxy and ethoxy.

In one embodiment, R^3 or R^{3a} is halo, such as bromo, chloro or fluoro, and in particular chloro.

In a particular embodiment, n is 1 and R^3 or R^{3a} is halo such as chloro.

Suitably in formula (IA), m is 0.

Examples of ring A include made up of a group of formula $-CR^{22}=CR^{22}-CR^{22}=CR^{22}-$, $-N=CR^{22}-CR^{22}=CR^{22}-$, $-CR^{22}=N-CR^{22}=CR^{22}-$, $-CR^{22}=CR^{22}-N=CR^{22}-$, $-CR^{22}=CR^{22}-CR^{22}=N-$, $-N=CR^{22}-N=CR^{22}-$, $-CR^{22}=N-CR^{22}=N-$, $-N=CR^{22}-CR^{22}=N-$, $-N=N-CR^{22}=CR^{22}-$, $-CR^{22}=CR^{22}-N=N-$, $-CR^{22}=CR^{22}-O-$, $-O-CR^{22}=CR^{22}-$,$-CR^{22}=CR^{22}-S-$, $-S-CR^{22}=CR^{22}-$, $-CR^{22}H-CR^{22}H-O-$, $-O-CR^{22}H-CR^{22}H-$, $-CR^{22}H-CR^{22}H-S-$, $-S-CR^{22}H-CR^{22}H-$, $-O-CR^{22}H-O-$, $-O-CF_2-O-$, $-O-CR^{22}H-CR^{22}H-O-$, $-S-CR^{22}H-S-$, $-S-CR^{22}H-CR^{22}H-S-$, $-CR^{22}=CR^{22}-NR^{20}-$, $-NR^{20}-CR^{22}=CR^{22}-$, $-CR^{22}H-CR^{22}H-NR^{20}-$, $-NR^{20}-CR^{22}H-CR^{22}H-$, $-N=CR^{22}-NR^{20}-$, $-NR^{20}-CR^{22}=N-$, $-NR^{20}-CR^{22}H-NR^{20}-$, $-OCR^{22}=N-$, $-N=CR^{22}-O-$, $-S-CR^{22}=N-$, $-N=CR^{22}-S-$,

-O-CR^{22}H-NR^{20}-, -NR^{20}-CR^{22}H-O-, -S-CR^{22}H-NR^{20}-, -NR^{20}-CR^{22}H-S-, -O-N=CR^{22}-, -CR^{22}=N-O-, -S-N=CR^{22}-, -CR^{22}=N-S-, -O-NR^{20}-CR^{22}H-, -CR^{22}H-NR^{20}-O-, -S-NR^{20}-CR^{22}H-, -CR^{22}H-NR^{20}-S-, -NR^{20}-N=CR^{22}-, -CR^{22}=N-NR^{20}-, -NR^{20}-NR^{20}-CR^{22}H-, -CR^{22}H-NR^{20}-NR^{20}-, -N=N-NR^{20}- or –NR^{20}-N=N-, where each R^{20} is independently selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl, and where each R^{22} is independently selected from hydrogen, halo or C_{1-6}alkyl.

In a particular embodiment, where a group A includes more than one group R^{20} or R^{22}, at least one such group is hydrogen.

Particular examples of groups R^{20} include hydrogen, methyl, ethyl or methylcarbonyl, in particular hydrogen.

Particular examples of groups R^{22} include hydrogen, chloro, fluoro, methyl or ethyl, in particular hydrogen.

In a particular embodiment, ring A is a fused five-membered ring. Thus particular examples of A are Ring A is made up of a group of formula -CH=CH-O-, -O-CH=CH-, -CH=CH-S-, -S-CH=CH-, -CH_2-CH_2-O-, -O-CH_2-CH_2-, -CH_2-CH_2-S-, -S-CH_2-CH_2-, -O-CH_2-O-, -O-CH_2-CH_2-O-, -S-CH_2-S-, -S-CH_2-CH_2-S-, -CH=CH-NR^{20}-, -NR^{20}-CH=CH-, -CH_2-CH_2-NR^{20}-, -NR^{20}-CH_2-CH_2-, -N=CH-NR^{20}-, -NR^{20}-CH=N-, -NR^{20}-CH_2-NR^{20}-, -OCH=N-, -N=CH-O-, -S-CH=N-, -N=CH-S-, -O-CH_2-NR^{20}-, -NR^{20}-CH_2-O-, -S-CH_2-NR^{20}-, -NR^{20}-CH_2-S-, -O-N=CH-, -CH=N-O-, -S-N=CH-, -CH=N-S-, -O-NR^{20}-CH_2-, -CH_2-NR^{20}-O-, -S-NR^{20}-CH_2-, -CH_2-NR^{20}-S-, -NR^{20}-N=CH-, -CH=N-NR^{20}-, -NR^{20}-NR^{20}-CH_2-, -CH_2-NR^{20}-NR^{20}-, -N=N-NR^{20}- or –NR^{20}-N=N-.

Particular examples of R^{20} include hydrogen, methyl, and acetyl. For instance, R^{20} is hydrogen.

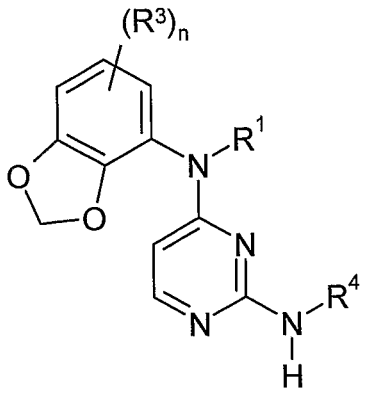
In one embodiment, Ring A includes one nitrogen atom. For instance, it is a group of formula -CH=CH-NR^{20}- or -NR^{20}-CH=CH-.

Ring A may also include two nitrogen atoms. For instance, it may be a group of formula -NR^{20}-N=CH-, -CH=N-NR^{20}-, -NR^{20}-NR^{20}-CH_2-, or -CH_2-NR^{20}-NR^{20} and in particular is a group -NR^{20}-N=CH- or -CH=N-NR^{20}-.

In another embodiment, Ring A includes one nitrogen and one oxygen atom. It is therefore suitably selected from -O-N=CH-, -CH=N-O-, -O-NR^{20}-CH_2- or -CH_2-NR^{20}-O-.

In yet a further embodiment, Ring A is a group of formula -O-CH_2-O- or -O-CF_2-O-, in particular -O-CH_2-O-.

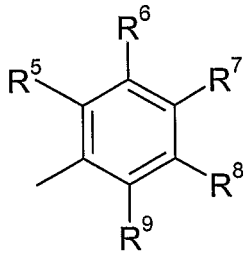
In particular, examples of compounds of formula (I) are compounds of formula (IB)



(IB)

wherein R^1, R^3, R^4 and n are as defined.

Particular examples of optionally substituted phenyl groups R^4 are groups of sub-formula (iii)



(iii)

where R^5, R^6, R^7, R^8 and R^9 are independently selected from:

(a) hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl), heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl);

(b) a group of sub-formula (iv):

$$-X^2-R^{14} \qquad \text{(iv)}$$

where X^2 is selected from O, NR^{16} S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{16})$, $CON(R^{16})$, $N(R^{16})CO$, $-N(R^{16})C(O)N(R^{16})-$, $-N(R^{16})C(O)O-$ $SO_2N(R^{16})$, $N(R^{16})SO_2$, $C(R^{16})_2O$, $C(R^{16})_2S$ and $N(R^{16})C(R^{16})_2$, where each R^{16} is independently selected from hydrogen or C_{1-6}alkyl,

R^{14} is hydrogen, C_{1-6} alkyl, trifluoromethyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl) or heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl);

(c) a group of sub-formula (v):

$$-X^3-R^{15}-Z \qquad (v)$$

where X^3 is a direct bond or is selected from O, NR^{17} S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{17})$, $CON(R^{17})$, $N(R^{17})CO$, $-N(R^{17})C(O)N(R^{17})-$, $-N(R^{17})C(O)O-$, $SO_2N(R^{17})$, $N(R^{17})SO_2$, $C(R^{17})_2O$, $C(R^{17})_2S$ and $N(R^{17})C(R^{17})_2$, where each R^{17} is independently selected from hydrogen or C_{1-6}alkyl;

R^{15} is a C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene, arylene, C_{3-12} carbocyclyl, heterocyclyl (including heteroaryl), any of which may be optionally substituted by one or more groups selected from halo, hydroxy, C_{1-6}alkoxy, cyano, amino, C_{1-6}alkylamino or di-(C_{1-6}alkyl)amino;

Z is halo, trifluoromethyl, cyano, nitro, aryl, C_{3-12} carbocyclyl or heterocyclyl (including heteroaryl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl and C_{1-6}alkoxy and wherein any heterocyclyl group within Z optionally bears 1 or 2 oxo substituents, or Z is a group of sub-formula (vi)

$$-X^4-R^{18} \qquad (vi)$$

where X^4 is selected from O, NR^{19} S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{19})$, $CON(R^{19})$, $N(R^{19})CO$, $SO_2N(R^{19})$, $-N(R^{19})C(O)N(R^{19})-$, $-N(R^{19})C(O)O-$ $N(R^{19})SO_2$, $C(R^{19})_2O$, $C(R^{19})_2S$ and $N(R^{19})C(R^{19})_2$, where each R^{19} is independently selected from hydrogen or C_{1-6}alkyl; and R^{18} is selected from hydrogen, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl) or heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl and C_{1-6}alkoxy, and wherein any heterocyclyl group within R^{18} optionally bears 1 or 2 oxo substituents; or

(d) R^5 and R^6, R^6 and R^7, R^7 and R^8 or R^8 and R^9 are joined together to form a fused ring, which is optionally substituted, and which may contain one or more heteroatoms selected from oxygen, sulphur or nitrogen, where sulphur atoms may

be optionally oxidised to a sulphur oxide, where any CH_2 groups may be substituted by a C(O) group, and where nitrogen atoms, depending upon valency considerations, may be substituted by a group R^{21}, where R^{21} is selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl.

In particular at least one, for instance at least two, of R^5, R^6, R^7, R^8 and R^9 are hydrogen. In one embodiment, at least three of R^5, R^6, R^7, R^8 and R^9 are hydrogen.

In one embodiment, at least one of R^5, R^6, R^7, R^8 and R^9 is other than hydrogen. In a particular embodiment, at least one of R^6, R^7 or R^8 is other than hydrogen.

Particular examples of R^5, R^6, R^7, R^8 and R^9, where these are other than hydrogen include halo, trifluoromethoxy, cyano, C_{2-8}alkynyl, heterocyclyl ,

a group of sub-formula (iv)

$$-X^2-R^{14} \qquad \text{(iv)}$$

where X^2 is selected from O, NR^{16}, SO_2, $CON(R^{16})$, $N(R^{16})CO$, $SO_2N(R^{16})$, $N(R^{16})SO_2$, where each R^{16} is independently selected from hydrogen or C_{1-6}alkyl, and R^{14} is hydrogen, C_{1-6} alkyl or trifluoromethyl,

or a group of sub-formula (v) :

$$-X^3-R^{15}-Z \qquad \text{(v)}$$

where X^3 is a direct bond or is selected from O, $CON(R^{17})$, $N(R^{17})CO$, $SO_2N(R^{17})$, $N(R^{17})SO_2$, where each R^{17} is independently selected from hydrogen or C_{1-6}alkyl, and in particular is hydrogen,

R^{15} is a C_{1-6}alkylene, and

Z is cyano, or heterocyclyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo or C_{1-6}alkyl, or Z is a group of sub-formula (vi)

$$-X^4-R^{18} \qquad \text{(vi)}$$

where X^4 is selected from O, NR^{19} $CON(R^{19})$, $N(R^{19})CO$, $SO_2N(R^{19})$ or $N(R^{19})SO_2$, where each R^{19} is independently selected from hydrogen or C_{1-6}alkyl; and R^{18} is selected from hydrogen, C_{1-6} alkyl, or heterocyclyl.

Particular examples of heterocyclic groups for R^5, R^6, R^7, R^8 and R^9 as well as Z include saturated five or six membered rings which contain at least one nitrogen atom and optionally also one or more further heteroatoms selected from oxygen, nitrogen and sulphur. These may be linked either to the phenyl ring in the case of R^5, R^6, R^7, R^8 and R^9 or to the group R^{15} in the case of Z via a carbon or nitrogen atom. In a particular

embodiment, at least one of R^5, R^6, R^7, R^8 and R^9 or Z is an N-linked heterocyclic group. Particular examples of such groups include pyrrolidine and N-morpholino.

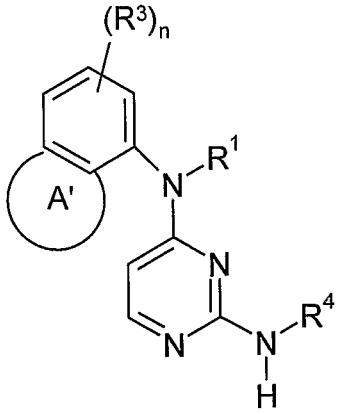
Specific examples of groups R^5, R^6, R^7, R^8 or R^9 where these are other than hydrogen include chloro, fluoro, methyl, methoxy, ethoxyethoxy trifluoromethoxy, ethynyl, cyano, hydroxymethyl, hydroxyethyl, cyanomethyl, amido, N-methylamido, N-(2-methoxyethyl)amido, 4-(pyridin-2-ylmethoxy), N-methylmethanesulfonamido, pyrrolidin-1-ylethoxy, morpholino, 2-morpholin-4-ylethoxy, 2-hydroxyethyl)-N-methylsulfonamido, diethylaminoethylamido, 4-methylpiperazin-1-yl)ethoxy, fluorobenzyloxy, sulfonamido, methanesulfonamido, methoxyethylsulfonamido, acetamido, N-methylacetamido, methylacetamidomethyl, methylsulfonyl and dimethylamino.

Where R^5 and R^6, R^6 and R^7, R^7 and R^8 or R^8 and R^9 are joined to form a fused ring, the ring suitably includes at least one heteroatom. In particular, a fused ring formed by R^5 and R^6, R^6 and R^7, R^7 and R^8 or R^8 and R^9 contains one or two nitrogen atoms or one nitrogen atom and one sulphur atom. Suitably the ring includes 5 ring atoms including the carbon atoms to which R^5 and R^6, R^6 and R^7, R^7 and R^8 or R^8 and R^9 are attached.

Fused rings formed by R^5 and R^6, R^6 and R^7, R^7 and R^8 or R^8 and R^9 may carry optional substituents which may be selected from those listed above for R^3.

Particular examples of fused rings include formed by R^5 and R^6, R^6 and R^7, R^7 and R^8 or R^8 and R^9 and the phenyl ring to which they are attached include indolyl, indazolyl, indolone and benzothiazolyl.

In another embodiment, the invention provides a compound of formula (IC)



(IC)

where R^1, R^3, R^4 and n are as defined herein relation to formula (I) and A' is selected from a group $-OCH_2O-$, $-OCF_2O-$, $-CH=CH-NR^{20}-$ or $-NR^{20}-CH=CH-$, $-O-N=CH-$, $-CH=N-O-$, $-O-NR^{20}-CH_2-$, $-CH_2-NR^{20}-O-$, $-NR^{20}-N=CH-$, $-CH=N-NR^{20}-$, $-NR^{20}-NR^{20}-CH_2-$ or $-CH_2-NR^{20}-NR^{20}$.

In particular, A' is a selected from $-OCH_2O-$, $-OCF_2O-$, $-CH=CH-NR^{20}-$, $-NR^{20}-CH=CH-$, $-O-N=CH-$, $-CH=N-O-$, $-O-NR^{20}-CH_2-$, $-CH_2-NR^{20}-O-$, $-NR^{20}-N=CH-$ or $-CH=N-NR^{20}-$.

Particular examples of compounds of formula (IC) are compounds of formula (IB) as set out above, and these form a particular aspect of the invention.

Particular options for R^1, R^3, R^4 n and R^{20} in formula (IC) are as set out herein in relation to formula (I). In particular, compounds of formula (IB) form a particular aspect of the invention.

Particular novel compounds of the invention include, for example, compounds of Formula (I), or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of R^1, R^2, R^3, ring A, n or R^4 has any of the meanings defined hereinbefore or in paragraphs (1) to (34) hereinafter:-

1. Ring A is selected from: $-CR^{22}=CR^{22}-CR^{22}=CR^{22}-$, $-N=CR^{22}-CR^{22}=CR^{22}-$, $-CR^{22}=N-CR^{22}=CR^{22}-$, $-CR^{22}=CR^{22}-N=CR^{22}-$, $-CR^{22}=CR^{22}-CR^{22}=N-$, $-N=CR^{22}-N=CR^{22}-$, $-CR^{22}=N-CR^{22}=N-$, $-N=CR^{22}-CR^{22}=N-$, $-N=N-CR^{22}=CR^{22}-$, $-CR^{22}=CR^{22}-N=N-$, $-CR^{22}=CR^{22}-O-$, $-O-CR^{22}=CR^{22}-$, $-CR^{22}=CR^{22}-S-$, $-S-CR^{22}=CR^{22}-$, $-CR^{22}H-CR^{22}H-O-$, $-O-CR^{22}H-CR^{22}H-$, $-CR^{22}H-CR^{22}H-S-$, $-S-CR^{22}H-CR^{22}H-$, $-O-CR^{22}H-O-$, $-O-CF_2-O-$, $-O-CR^{22}H-CR^{22}H-O-$, $-S-CR^{22}H-S-$, $-S-CR^{22}H-CR^{22}H-S-$, $-CR^{22}=CR^{22}-NR^{20}-$, $-NR^{20}-CR^{22}=CR^{22}-$, $-CR^{22}H-CR^{22}H-NR^{20}-$, $-NR^{20}-CR^{22}H-CR^{22}H-$, $-N=CR^{22}-NR^{20}-$, $-NR^{20}-CR^{22}=N-$, $-NR^{20}-CR^{22}H-NR^{20}-$, $-OCR^{22}=N-$, $-N=CR^{22}-O-$, $-S-CR^{22}=N-$, $-N=CR^{22}-S-$, $-O-CR^{22}H-NR^{20}-$, $-NR^{20}-CR^{22}H-O-$, $-S-CR^{22}H-NR^{20}-$, $-NR^{20}-CR^{22}H-S-$, $-O-N=CR^{22}-$, $-CR^{22}=N-O-$, $-S-N=CR^{22}-$, $-CR^{22}=N-S-$, $-O-NR^{20}-CR^{22}H-$, $-CR^{22}H-NR^{20}-O-$, $-S-NR^{20}-CR^{22}H-$, $-CR^{22}H-NR^{20}-S-$, $-NR^{20}-N=CR^{22}-$, $-CR^{22}=N-NR^{20}-$, $-NR^{20}-NR^{20}-CR^{22}H-$, $-CR^{22}H-NR^{20}-NR^{20}-$, $-N=N-NR^{20}-$, or $-NR^{20}-N=N-$, where each R^{20} is independently selected from hydrogen, C_{1-4}alkyl or C_{1-4}alkylcarbonyl, and where each R^{22} is independently selected from hydrogen,

halo, cyano, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, -$S(O)_z$-C_{1-4}alkyl (where z is 0, 1 or 2), or –NR^aR^b (where R^a and R^b are each independently selected from hydrogen, C_{1-2}alkyl, or C_{1-2}alkanoyl).

2. Ring A is selected from -N=CR^{22}-CR^{22}=CR^{22}-, -CR^{22}=N-CR^{22}=CR^{22}-, -CR^{22}=CR^{22}-N=CR^{22}-, -CR^{22}=CR^{22}-CR^{22}=N-, -CR^{22}=CR^{22}-O-, -O-CR^{22}=CR^{22}-, -O-CR^{22}H-O-, -O-CF_2-O-, -O-CR^{22}H-CR^{22}H-O-, -CR^{22}=CR^{22}-NR^{20} -, -NR^{20}-CR^{22}=CR^{22}-, -CR^{22}H-CR^{22}H-NR^{20}-, -NR^{20}-CR^{22}H-CR^{22}H-, -OCR^{22}=N-, -N=CR^{22}-O-, -S-CR^{22}=N-, -N=CR^{22}-S-, -NR^{20}-N=CR^{22}-, or -CR^{22}=N-NR^{20}-, where each R^{20} is independently selected from hydrogen, C_{1-2}alkyl or C_{1-2}alkylcarbonyl, and where each R^{22} is independently selected from hydrogen, halo, cyano, hydroxy, C_{1-2}alkyl, C_{1-2}alkoxy, -$S(O)_z$-C_{1-2}alkyl (where z is 0, 1 or 2), or –NR^aR^b (where R^a and R^b are each independently selected from hydrogen, C_{1-2}alkyl, or C_{1-2}alkanoyl).

3. Ring A is selected from -O-CR^{22}H-O-, -O-CF_2-O-, -OCR^{22}=N-, -N=CR^{22}-O-, -S-CR^{22}=N-, -N=CR^{22}-S-, -NR^{20}-N=CR^{22}-, or -CR^{22}=N-NR^{20}-, where each R^{20} is independently selected from hydrogen, C_{1-2}alkyl or C_{1-2}alkylcarbonyl, and where each R^{22} is independently selected from hydrogen, halo, cyano, hydroxy, C_{1-2}alkyl, C_{1-2}alkoxy, -$S(O)_z$-C_{1-2}alkyl (where z is 0, 1 or 2), or –NR^aR^b (where R^a and R^b are each independently selected from hydrogen, C_{1-2}alkyl, or C_{1-2}alkanoyl).

4. Ring A is selected from -O-CR^{22}H-O-, -O-CF_2-O-, -OCR^{22}=N-, -N=CR^{22}-O-, -S-CR^{22}=N-, -N=CR^{22}-S-, -NR^{20}-N=CR^{22}-, or -CR^{22}=N-NR^{20}-, where each R^{20} is independently selected from hydrogen, or C_{1-2}alkyl, and where each R^{22} is independently selected from hydrogen, halo, or methyl.

5. Ring A is selected from: -CR^{22}=CR^{22}-CR^{22}=CR^{22}-, -N=CR^{22}-CR^{22}=CR^{22}-, -CR^{22}=N-CR^{22}=CR^{22}-, -CR^{22}=CR^{22}-N=CR^{22}-, -CR^{22}=CR^{22}-CR^{22}=N-, -N=CR^{22}-N=CR^{22}-, -CR^{22}=N-CR^{22}=N-, -N=CR^{22}-CR^{22}=N-, -N=N-CR^{22}=CR^{22}-, -CR^{22}=CR^{22}-N=N-, -CR^{22}=CR^{22}-O-, -O-CR^{22}=CR^{22}-, -CR^{22}=CR^{22}-S-, -S-CR^{22}=CR^{22}-, -CR^{22}H-CR^{22}H-O-, -O-CR^{22}H-CR^{22}H-, -CR^{22}H-CR^{22}H-S-, -S-CR^{22}H-CR^{22}H-, -O-CR^{22}H-O-, -O-CF_2-O-, -O-CR^{22}H-CR^{22}H-O-, -S-CR^{22}H-S-,

-S-CR^{22}H-CR^{22}H-S-, -CR^{22}=CR^{22}-NR^{20} -, -NR^{20}-CR^{22}=CR^{22}-, -CR^{22}H-CR^{22}H-NR^{20}-, -NR^{20}-CR^{22}H-CR^{22}H-, -N=CR^{22}-NR^{20}-, -NR^{20}-CR^{22}=N-, -NR^{20}-CR^{22}H-NR^{20}-, -OCR^{22}=N-, -N=CR^{22}-O-, -S-CR^{22}=N-, -N=CR^{22}-S-, -O-CR^{22}H-NR^{20}-, -NR^{20}-CR^{22}H-O-, -S-CR^{22}H-NR^{20}-, -NR^{20}-CR^{22}H-S-, -O-N=CR^{22}-, -CR^{22}=N-O-, -S-N=CR^{22}-, -CR^{22}=N-S-, -O-NR^{20}-CR^{22}H-, -CR^{22}H-NR^{20}-O-, -S-NR^{20}-CR^{22}H-, -CR^{22}H-NR^{20}-S-, -NR^{20}-NR^{20}-CR^{22}H-, -CR^{22}H-NR^{20}-NR^{20}-, -N=N-NR^{20}-, or -NR^{20}-N=N-, where each R^{20} is independently selected from hydrogen, C_{1-4}alkyl or C_{1-4}alkylcarbonyl, and where each R^{22} is independently selected from hydrogen, halo, cyano, hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, -$S(O)_z$-C_{1-4}alkyl (where z is 0, 1 or 2), or –NR^aR^b (where R^a and R^b are each independently selected from hydrogen, C_{1-2}alkyl, or C_{1-2}alkanoyl).

6. Ring A is selected from -N=CR^{22}-CR^{22}=CR^{22}-, -CR^{22}=N-CR^{22}=CR^{22}-, -CR^{22}=CR^{22}-N=CR^{22}-, -CR^{22}=CR^{22}-CR^{22}=N-, -CR^{22}=CR^{22}-O-, -O-CR^{22}=CR^{22}-, -O-CR^{22}H-O-, -O-CF_2-O-, -O-CR^{22}H-CR^{22}H-O-, -CR^{22}=CR^{22}-NR^{20} -, -NR^{20}-CR^{22}=CR^{22}-, -CR^{22}H-CR^{22}H-NR^{20}-, -NR^{20}-CR^{22}H-CR^{22}H-, -OCR^{22}=N-, -N=CR^{22}-O-, -S-CR^{22}=N-, or -N=CR^{22}-S-, where each R^{20} is independently selected from hydrogen, C_{1-2}alkyl or C_{1-2}alkylcarbonyl, and where each R^{22} is independently selected from hydrogen, halo, cyano, hydroxy, C_{1-2}alkyl, C_{1-2}alkoxy, -$S(O)_z$-C_{1-2}alkyl (where z is 0, 1 or 2), or –NR^aR^b (where R^a and R^b are each independently selected from hydrogen, C_{1-2}alkyl, or C_{1-2}alkanoyl).

7. Ring A is selected from -O-CR^{22}H-O-, -O-CF_2-O-, -OCR^{22}=N-, -N=CR^{22}-O-, -S-CR^{22}=N-, or -N=CR^{22}-S-, where each R^{20} is independently selected from hydrogen, C_{1-2}alkyl or C_{1-2}alkylcarbonyl, and where each R^{22} is independently selected from hydrogen, halo, cyano, hydroxy, C_{1-2}alkyl, C_{1-2}alkoxy, -$S(O)_z$-C_{1-2}alkyl (where z is 0, 1 or 2), or –NR^aR^b (where R^a and R^b are each independently selected from hydrogen, C_{1-2}alkyl, or C_{1-2}alkanoyl).

8. Ring A is selected from -O-CR^{22}H-O-, -O-CF_2-O-, -OCR^{22}=N-, -N=CR^{22}-O-, -S-CR^{22}=N-, or -N=CR^{22}-S-, where each R^{20} is independently selected from hydrogen, or C_{1-2}alkyl, and where each R^{22} is independently selected from hydrogen, halo, or methyl.

9. R^1 is hydrogen or a C_{1-4}alkyl group which is optionally substituted with one or more substituents selected from cyano, –OR^2, –$NR^{2a}R^{2b}$, -C(O)$NR^{2a}R^{2b}$, or -$N(R^{2a})C(O)R^2$, halo or haloC_{1-4}alkyl (such as trifluoromethyl), where R^2, R^{2a} and R^{2b} are selected from hydrogen or C_{1-4}alkyl;

10. R^1 is hydrogen or a C_{1-2}alkyl group, which is optionally substituted with one or more substituents selected from cyano, –OR^2, –$NR^{2a}R^{2b}$, -C(O)$NR^{2a}R^{2b}$, or -$N(R^{2a})C(O)R^2$, halo or haloC_{1-4}alkyl (such as trifluoromethyl), where R^2, R^{2a} and R^{2b} are selected from hydrogen or C_{1-4}alkyl;

11. R^1 is hydrogen or a C_{1-2}alkyl group, which is optionally substituted with one or more substituents selected from cyano, –OR^2, –$NR^{2a}R^{2b}$, where R^2, R^{2a} and R^{2b} are selected from hydrogen or C_{1-2}alkyl;

12. R^1 is hydrogen or a C_{1-2}alkyl group;

13. R^1 is hydrogen;

14. R^1 is a C_{1-2}alkyl group, which is optionally substituted with one or more substituents selected from cyano, –OR^2, –$NR^{2a}R^{2b}$, where R^2, R^{2a} and R^{2b} are selected from hydrogen or C_{1-2}alkyl;

15. R^1 is a C_{1-2}alkyl group;

16. R^1 is methyl;

17. **n** is 0, 1, or 2;

18. **n** is 0 or 1;

19. n is 0;

20. n is 1;

21. each group $\mathbf{R^3}$ present is independently selected from halo, trifluoromethyl, cyano, nitro or a group of sub-formula (i) :

$$-X^1-R^{11} \qquad (i)$$

where $\mathbf{X^1}$ is selected from a direct bond or O, S, SO, SO_2, OSO_2, NR^{13}, CO, $CH(OR^{13})$, $CONR^{13}$, $N(R^{13})CO$, $SO_2N(R^{13})$, $N(R^{13})SO_2$, $C(R^{13})_2O$, $C(R^{13})_2S$, $C(R^{13})_2N(R^{13})$ and $N(R^{13})C(R^{13})_2$, wherein $\mathbf{R^{13}}$ is hydrogen or C_{1-6}alkyl and $\mathbf{R^{11}}$ is selected from hydrogen, or C_{1-6} alkyl, which may be optionally substituted with one or more groups selected from halo, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, and C_{1-6}alkoxy;

22. each group $\mathbf{R^3}$ present is independently selected from halo, trifluoromethyl, cyano, nitro or a group of sub-formula (i) :

$$-X^1-R^{11} \qquad (i)$$

where $\mathbf{X^1}$ is selected from a direct bond or O, NR^{13}, CO, $CONR^{13}$, $N(R^{13})CO$, wherein $\mathbf{R^{13}}$ is hydrogen or C_{1-4}alkyl and $\mathbf{R^{11}}$ is selected from hydrogen or C_{1-4}alkyl, which may be optionally substituted with one or more groups selected from halo, cyano, or C_{1-4}alkoxy;

23. each group $\mathbf{R^3}$ present is independently selected from halo, trifluoromethyl, cyano, nitro or a group of sub-formula (i) :

$$-X^1-R^{11} \qquad (i)$$

where $\mathbf{X^1}$ is selected from a direct bond or O, $CONR^{13}$, wherein $\mathbf{R^{13}}$ is hydrogen or C_{1-6}alkyl and $\mathbf{R^{11}}$ is selected from hydrogen or C_{1-4}alkyl, which may be optionally substituted with one or more C_{1-2}alkoxy groups;

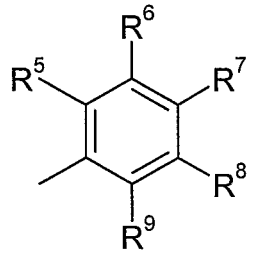
24. each group $\mathbf{R^3}$ present is independently selected from halo or a group of sub-formula (i) :

$$-X^1-R^{11} \qquad \text{(i)}$$

where $\mathbf{X^1}$ is selected from a direct bond or O, $CONR^{13}$, wherein $\mathbf{R^{13}}$ is hydrogen or C_{1-6}alkyl and $\mathbf{R^{11}}$ is selected from hydrogen, C_{1-2}alkyl, any of which may be optionally substituted with one or more C_{1-2}alkoxy groups;

25. each group $\mathbf{R^3}$ present is independently selected from fluoro, chloro, cyano, $-CONH_2$, or C_{1-2}alkyl optionally substituted by C_{1-2}alkoxy;

26. R^4 is a group of sub-formula (iii)



(iii)

where R^5, R^6, R^7, R^8 and R^9 are independently selected from:

(a) hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl), heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) and wherein any aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl), heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) groups are optionally substituted on any available carbon atoms by halo, hydroxy, cyano, amino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino and any nitrogen atoms present in the heterocyclyl moieties may, depending

upon valency considerations, be substituted by a group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl, and where any sulphur atoms may be optionally oxidised to a sulphur oxide;

(b) a group of sub-formula (iv);

$$-X^2-R^{14} \qquad \text{(iv)}$$

where X^2 is selected from O, NR^{16}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{16})$, $CON(R^{16})$, $N(R^{16})CO$, $-N(R^{16})C(O)N(R^{16})-$, $-N(R^{16})C(O)O-$, $SON(R^{16})$, $N(R^{16})SO$, $SO_2N(R^{16})$, $N(R^{16})SO_2$, $C(R^{16})_2O$, $C(R^{16})_2S$ and $N(R^{16})C(R^{16})_2$, where each R^{16} is independently selected from hydrogen or C_{1-6}alkyl,

R^{14} is hydrogen, C_{1-6} alkyl, trifluoromethyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, or a 4- to 8-membered mono or bicyclic heterocyclyl ring (including 5 or 6 membered heteroaryl rings) or 4- to 8-membered mono or bicyclic heterocyclyl-C_{1-6}alkyl groups (including 5 or 6 membered heteroaryl-C_{1-6}alkyl groups) and wherein any aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl), heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) groups are optionally substituted on any available carbon atoms by oxo, halo, cyano, amino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino and any nitrogen atoms present in the heterocyclyl moieties may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl, and where any sulphur atoms may be optionally oxidised to a sulphur oxide;

(c) a group of sub-formula (v):

$$-X^3-R^{15}-Z \qquad \text{(v)}$$

where X^3 is a direct bond or is selected from O, NR^{17}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{17})$, $CON(R^{17})$, $N(R^{17})CO$, $-N(R^{17})C(O)N(R^{17})-$, $-N(R^{17})C(O)O-$, $SO_2N(R^{17})$, $N(R^{17})SO_2$, $C(R^{17})_2O$, $C(R^{17})_2S$ and $N(R^{17})C(R^{17})_2$, where each R^{17} is independently selected from hydrogen or C_{1-6}alkyl;

R^{15} is a C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene, arylene, C_{3-12} carbocyclyl, heterocyclyl (including heteroaryl), any of which may be

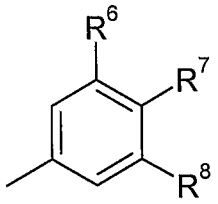
optionally substituted by one or more groups selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, amino, C_{1-6}alkylamino or di-(C_{1-6}alkyl)amino; Z is halo, trifluoromethyl, cyano, nitro, aryl, C_{3-12} carbocyclyl or heterocyclyl (including heteroaryl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl and C_{1-6}alkoxy and wherein any heterocyclyl group within Z optionally bears 1 or 2 oxo substituents, or Z is a group of sub-formula (vi)

$$-X^4-R^{18} \qquad \text{(vi)}$$

where X^4 is selected from O, NR^{19}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{19})$, $CON(R^{19})$, $N(R^{19})CO$, $SO_2N(R^{19})$, $-N(R^{19})C(O)N(R^{19})-$, $-N(R^{19})C(O)O-$ $N(R^{19})SO_2$, $C(R^{19})_2O$, $C(R^{19})_2S$ and $N(R^{19})C(R^{19})_2$, where each R^{19} is independently selected from hydrogen or C_{1-6}alkyl; and R^{18} is selected from hydrogen, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl) or heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl and C_{1-6}alkoxy, and wherein any heterocyclyl group within R^{18} optionally bears 1 or 2 oxo substituents; or

(d) R^5 and R^6, R^6 and R^7, R^7 and R^8 or R^8 and R^9 are joined together to form a fused 5-, 6- or 7-membered saturated or unsaturated ring, which is optionally substituted on any available carbon atom by halo, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, amino, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino, and which may contain one or more heteroatoms selected from oxygen, sulphur or nitrogen, where sulphur atoms may be optionally oxidised to a sulphur oxide, where any CH_2 groups may be substituted by a C(O) group, and where nitrogen atoms, depending upon valency considerations, may be substituted by a group R^{21}, where R^{21} is selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl;

27. R^4 is a group of sub-formula (iiia)



(iiia)

where R^6, R^7, and R^8 are independently selected from:

(a) hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl), heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) and wherein any aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl), heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) groups are optionally substituted on any available carbon atoms by halo, hydroxy, cyano, amino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino and any nitrogen atoms present in the heterocyclyl moieties may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl, and where any sulphur atoms may be optionally oxidised to a sulphur oxide;

(b) a group of sub-formula (iv):

$$-X^2-R^{14} \qquad \text{(iv)}$$

where X^2 is selected from O, NR^{16}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{16})$, $CON(R^{16})$, $N(R^{16})CO$, $-N(R^{16})C(O)N(R^{16})-$, $-N(R^{16})C(O)O-$, $SON(R^{16})$, $N(R^{16})SO$, $SO_2N(R^{16})$, $N(R^{16})SO_2$, $C(R^{16})_2O$, $C(R^{16})_2S$ and $N(R^{16})C(R^{16})_2$, where each R^{16} is independently selected from hydrogen or C_{1-6}alkyl,

R^{14} is hydrogen, C_{1-6} alkyl, trifluoromethyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, or a 4- to 8-membered mono or bicyclic heterocyclyl ring (including 5 or 6 membered heteroaryl rings) or 4- to 8-membered mono or bicyclic heterocyclyl-C_{1-6}alkyl groups (including 5 or 6

membered heteroaryl-C_{1-6}alkyl groups) and wherein any aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl), heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) groups are optionally substituted on any available carbon atoms by oxo, halo, cyano, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino and any nitrogen atoms present in the heterocyclyl moieties may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl, and where any sulphur atoms may be optionally oxidised to a sulphur oxide;

(c) a group of sub-formula (v):

$$-X^3-R^{15}-Z \qquad (v)$$

where X^3 is a direct bond or is selected from O, NR^{17}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{17})$, $CON(R^{17})$, $N(R^{17})CO$, $-N(R^{17})C(O)N(R^{17})-$, $-N(R^{17})C(O)O-$, $SO_2N(R^{17})$, $N(R^{17})SO_2$, $C(R^{17})_2O$, $C(R^{17})_2S$ and $N(R^{17})C(R^{17})_2$, where each R^{17} is independently selected from hydrogen or C_{1-6}alkyl;

R^{15} is a C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene, arylene, C_{3-12} carbocyclyl, heterocyclyl (including heteroaryl), any of which may be optionally substituted by one or more groups selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, amino, C_{1-6}alkylamino or di-(C_{1-6}alkyl)amino;

Z is halo, trifluoromethyl, cyano, nitro, aryl, C_{3-12} carbocyclyl or heterocyclyl (including heteroaryl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl and C_{1-6}alkoxy and wherein any heterocyclyl group within Z optionally bears 1 or 2 oxo substituents, or Z is a group of sub-formula (vi)

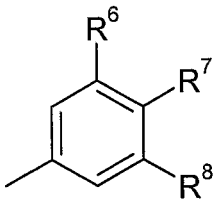
$$-X^4-R^{18} \qquad (vi)$$

where X^4 is selected from O, NR^{19}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{19})$, $CON(R^{19})$, $N(R^{19})CO$, $SO_2N(R^{19})$, $-N(R^{19})C(O)N(R^{19})-$, $-N(R^{19})C(O)O-$ $N(R^{19})SO_2$, $C(R^{19})_2O$, $C(R^{19})_2S$ and $N(R^{19})C(R^{19})_2$, where each R^{19} is independently selected from hydrogen or C_{1-6}alkyl; and R^{18} is selected from hydrogen, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12}

carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl) or heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl and C_{1-6}alkoxy, and wherein any heterocyclyl group within R^{18} optionally bears 1 or 2 oxo substituents; or

(d) R^6 and R^7, or R^7 and R^8 are joined together to form a fused 5-, 6- or 7-membered saturated or unsaturated ring, which is optionally substituted on any available carbon atom by halo, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, amino, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino, and which may contain one or more heteroatoms selected from oxygen, sulphur or nitrogen, where sulphur atoms may be optionally oxidised to a sulphur oxide, where any CH_2 groups may be substituted by a C(O) group, and where nitrogen atoms, depending upon valency considerations, may be substituted by a group R^{21}, where R^{21} is selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl.

28. R^4 is a group of sub-formula (iiia)



(iiia)

where R^6, R^7, and R^8 are independently selected from:

(a) hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, heterocyclyl (including heteroaryl), and wherein any aryl or heterocyclyl (including heteroaryl) groups are optionally substituted on any available carbon atoms by halo, hydroxy, cyano, amino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, and any nitrogen atoms present in the heterocyclyl moieties may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl;

(b) a group of sub-formula (iv):

$-X^2-R^{14}$ (iv)

where X^2 is selected from O, NR^{16}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{16})$, $CON(R^{16})$, $N(R^{16})CO$, $SON(R^{16})$, $N(R^{16})SO$, $SO_2N(R^{16})$, and $N(R^{16})SO_2$, where each R^{16} is independently selected from hydrogen or C_{1-6}alkyl,

R^{14} is hydrogen, C_{1-6} alkyl, trifluoromethyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, or a 4- to 8-membered mono or bicyclic heterocyclyl ring (including 5 or 6 membered heteroaryl rings) and wherein any aryl, C_{3-12} carbocyclyl, heterocyclyl (including heteroaryl) groups are optionally substituted on any available carbon atoms by oxo, halo, cyano, amino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino and any nitrogen atoms present in the heterocyclyl moieties may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl, and where any sulphur atoms may be optionally oxidised to a sulphur oxide;

(c) a group of sub-formula (v):

$-X^3-R^{15}-Z$ (v)

where X^3 is a direct bond or is selected from O, NR^{17}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CON(R^{17})$, $N(R^{17})CO$, $SO_2N(R^{17})$, and $N(R^{17})SO_2$, where each R^{17} is independently selected from hydrogen or C_{1-6}alkyl;

R^{15} is a C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene, arylene, C_{3-12} carbocyclyl, heterocyclyl (including heteroaryl), any of which may be optionally substituted by one or more groups selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, amino, C_{1-6}alkylamino or di-(C_{1-6}alkyl)amino;

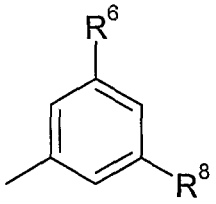
Z is halo, trifluoromethyl, cyano, nitro, aryl, or heterocyclyl (including heteroaryl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl and C_{1-6}alkoxy and wherein any heterocyclyl group within Z optionally bears 1 or 2 oxo substituents, or Z is a group of sub-formula (vi)

$-X^4-R^{18}$ (vi)

where X^4 is selected from O, NR^{19}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CON(R^{19})$, $N(R^{19})CO$, $SO_2N(R^{19})$, and $N(R^{19})SO_2$, where each R^{19} is

independently selected from hydrogen or C_{1-6}alkyl; and R^{18} is selected from hydrogen, C_{1-6} alkyl, aryl, or heterocyclyl (including heteroaryl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl, and C_{1-6}alkoxy, and wherein any heterocyclyl group within R^{18} optionally bears 1 or 2 oxo substituents;

29. R^4 is a group of sub-formula (iiib)



(iiib)

wherein at least one of R^6 and R^8 is a 5, 6, or 7-membered heterocyclic ring which is nitrogen-linked and the other is independently selected from:

(a) hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, heterocyclyl (including heteroaryl), and wherein any aryl or heterocyclyl (including heteroaryl) groups are optionally substituted on any available carbon atoms by halo, hydroxy, cyano, amino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, and any nitrogen atoms present in the heterocyclyl moieties may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl;

(b) a group of sub-formula (iv):

$$-X^2-R^{14} \qquad \text{(iv)}$$

where X^2 is selected from O, NR^{16}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{16})$, $CON(R^{16})$, $N(R^{16})CO$, $SON(R^{16})$, $N(R^{16})SO$, $SO_2N(R^{16})$, and $N(R^{16})SO_2$, where each R^{16} is independently selected from hydrogen or C_{1-6}alkyl,

R^{14} is hydrogen, C_{1-6} alkyl, trifluoromethyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, or a 4- to 8-membered mono or bicyclic heterocyclyl ring (including 5 or 6 membered heteroaryl rings) and wherein any aryl, C_{3-12}

carbocyclyl, heterocyclyl (including heteroaryl) groups are optionally substituted on any available carbon atoms by oxo, halo, cyano, amino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino and any nitrogen atoms present in the heterocyclyl moieties may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl, and where any sulphur atoms may be optionally oxidised to a sulphur oxide;

(c) a group of sub-formula (v):

$$-X^3-R^{15}-Z \qquad (v)$$

where X^3 is a direct bond or is selected from O, NR^{17}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CON(R^{17})$, $N(R^{17})CO$, $SO_2N(R^{17})$, and $N(R^{17})SO_2$, where each R^{17} is independently selected from hydrogen or C_{1-6}alkyl;

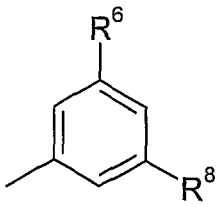
R^{15} is a C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene, arylene, C_{3-12} carbocyclyl, heterocyclyl (including heteroaryl), any of which may be optionally substituted by one or more groups selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, amino, C_{1-6}alkylamino or di-(C_{1-6}alkyl)amino;

Z is halo, trifluoromethyl, cyano, nitro, aryl, or heterocyclyl (including heteroaryl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl and C_{1-6}alkoxy and wherein any heterocyclyl group within Z optionally bears 1 or 2 oxo substituents, or Z is a group of sub-formula (vi)

$$-X^4-R^{18} \qquad (vi)$$

where X^4 is selected from O, NR^{19}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CON(R^{19})$, $N(R^{19})CO$, $SO_2N(R^{19})$, and $N(R^{19})SO_2$, where each R^{19} is independently selected from hydrogen or C_{1-6}alkyl; and R^{18} is selected from hydrogen, C_{1-6} alkyl, aryl, or heterocyclyl (including heteroaryl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl, and C_{1-6}alkoxy, and wherein any heterocyclyl group within R^{18} optionally bears 1 or 2 oxo substituents;

30. R^4 is a group of sub-formula (iiib)



(iiib)

wherein at least one of R^6 and R^8 is a 5 or 6-membered nitrogen-linked heterocyclic ring and the other is independently selected from:

(a) hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, heterocyclyl (including heteroaryl), and wherein any aryl or heterocyclyl (including heteroaryl) groups are optionally substituted on any available carbon atoms by halo, hydroxy, cyano, amino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, and any nitrogen atoms present in the heterocyclyl moieties may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl;

(b) a group of sub-formula (iv):

$$-X^2-R^{14} \qquad \text{(iv)}$$

where X^2 is selected from O, NR^{16}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{16})$, $CON(R^{16})$, $N(R^{16})CO$, $SON(R^{16})$, $N(R^{16})SO$, $SO_2N(R^{16})$, and $N(R^{16})SO_2$, where each R^{16} is independently selected from hydrogen or C_{1-6}alkyl,

R^{14} is hydrogen, C_{1-6} alkyl, trifluoromethyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, or a 4- to 8-membered mono or bicyclic heterocyclyl ring (including 5 or 6 membered heteroaryl rings) and wherein any aryl, C_{3-12} carbocyclyl, heterocyclyl (including heteroaryl) groups are optionally substituted on any available carbon atoms by oxo, halo, cyano, amino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino and any nitrogen atoms present in the heterocyclyl moieties may, depending upon valency considerations, be substituted by a

group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl, and where any sulphur atoms may be optionally oxidised to a sulphur oxide;

(c) a group of sub-formula (v) is

$$-X^3-R^{15}-Z \qquad (v)$$

where X^3 is a direct bond or is selected from O, NR^{17}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CON(R^{17})$, $N(R^{17})CO$, $SO_2N(R^{17})$, and $N(R^{17})SO_2$, where each R^{17} is independently selected from hydrogen or C_{1-6}alkyl;

R^{15} is a C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene, arylene, C_{3-12} carbocyclyl, heterocyclyl (including heteroaryl), any of which may be optionally substituted by one or more groups selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, amino, C_{1-6}alkylamino or di-(C_{1-6}alkyl)amino;

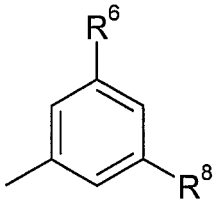
Z is halo, trifluoromethyl, cyano, nitro, aryl, or heterocyclyl (including heteroaryl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl and C_{1-6}alkoxy and wherein any heterocyclyl group within Z optionally bears 1 or 2 oxo substituents, or

Z is a group of sub-formula (vi)

$$-X^4-R^{18} \qquad (vi)$$

where X^4 is selected from O, NR^{19}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CON(R^{19})$, $N(R^{19})CO$, $SO_2N(R^{19})$, and $N(R^{19})SO_2$, where each R^{19} is independently selected from hydrogen or C_{1-6}alkyl; and R^{18} is selected from hydrogen, C_{1-6} alkyl, aryl, or heterocyclyl (including heteroaryl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl, and C_{1-6}alkoxy, and wherein any heterocyclyl group within R^{18} optionally bears 1 or 2 oxo substituents;

31. R^4 is a group of sub-formula (iiib)



(iiib)

wherein at least one of R^6 and R^8 is morpholin-4-yl and the other is independently selected from:

(a) hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, heterocyclyl (including heteroaryl), and wherein any aryl or heterocyclyl (including heteroaryl) groups are optionally substituted on any available carbon atoms by halo, hydroxy, cyano, amino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, and any nitrogen atoms present in the heterocyclyl moieties may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl;

(b) a group of sub-formula (iv):

$$-X^2-R^{14} \qquad \text{(iv)}$$

where X^2 is selected from O, NR^{16}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{16})$, $CON(R^{16})$, $N(R^{16})CO$, $SON(R^{16})$, $N(R^{16})SO$, $SO_2N(R^{16})$, and $N(R^{16})SO_2$, where each R^{16} is independently selected from hydrogen or C_{1-6}alkyl,

R^{14} is hydrogen, C_{1-6} alkyl, trifluoromethyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, or a 4- to 8-membered mono or bicyclic heterocyclyl ring (including 5 or 6 membered heteroaryl rings) and wherein any aryl, C_{3-12} carbocyclyl, heterocyclyl (including heteroaryl) groups are optionally substituted on any available carbon atoms by oxo, halo, cyano, amino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino and any nitrogen atoms present in the heterocyclyl moieties may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl, and where any sulphur atoms may be optionally oxidised to a sulphur oxide;

(c) a group of sub-formula (v):

$$-X^3-R^{15}-Z \qquad \text{(v)}$$

where X^3 is a direct bond or is selected from O, NR^{17}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CON(R^{17})$, $N(R^{17})CO$, $SO_2N(R^{17})$, and $N(R^{17})SO_2$, where each R^{17} is independently selected from hydrogen or C_{1-6}alkyl;

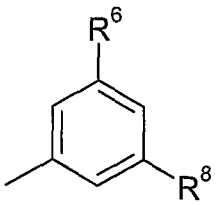
R^{15} is a C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene, arylene, C_{3-12} carbocyclyl, heterocyclyl (including heteroaryl), any of which may be optionally substituted by one or more groups selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, amino, C_{1-6}alkylamino or di-(C_{1-6}alkyl)amino;

Z is halo, trifluoromethyl, cyano, nitro, aryl, or heterocyclyl (including heteroaryl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl and C_{1-6}alkoxy and wherein any heterocyclyl group within Z optionally bears 1 or 2 oxo substituents, or Z is a group of sub-formula (vi)

$$-X^4-R^{18} \qquad \text{(vi)}$$

where X^4 is selected from O, NR^{19}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CON(R^{19})$, $N(R^{19})CO$, $SO_2N(R^{19})$, and $N(R^{19})SO_2$, where each R^{19} is independently selected from hydrogen or C_{1-6}alkyl; and R^{18} is selected from hydrogen, C_{1-6} alkyl, aryl, or heterocyclyl (including heteroaryl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl, and C_{1-6}alkoxy, and wherein any heterocyclyl group within R^{18} optionally bears 1 or 2 oxo substituents;

32. R^4 is a group of sub-formula (iiib)



(iiib)

wherein at least one of R^6 and R^8 is morpholin-4yl and the other is independently selected from:

(a) hydrogen, halo, trifluoromethyl, cyano, C_{1-4} alkyl, phenyl, a 5 or 6-membered heterocyclyl (including heteroaryl) comprising one or more heteroatoms selected from N, O or S,

and wherein any C_{1-4} alkyl, aryl or heterocyclyl (including heteroaryl) groups are optionally substituted on any available carbon atoms by halo,

hydroxy, cyano, amino, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkoxy, and any nitrogen atoms present in the heterocyclyl moieties may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-4}alkyl or C_{1-4}alkylcarbonyl; or

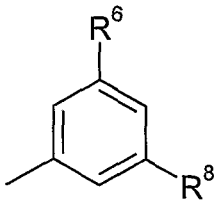
(b) a group of sub-formula (iv):

$$-X^2-R^{14} \qquad \text{(iv)}$$

where X^2 is selected from O, NR^{16}, S, SO, SO_2, OSO_2, CO, $CON(R^{16})$, $N(R^{16})CO$, $SON(R^{16})$, $N(R^{16})SO$, $SO_2N(R^{16})$, and $N(R^{16})SO_2$, where each R^{16} is independently selected from hydrogen or C_{1-4}alkyl,

R^{14} is hydrogen, or C_{1-4}alkyl;

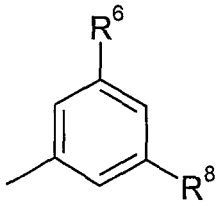
33. R^4 is a group of sub-formula (iiib)



(iiib)

wherein both R^6 and R^8 are 5 or 6-membered nitrogen-linked heterocyclylic rings;

34. R^4 is a group of sub-formula (iiib)



(iiib)

wherein both R^6 and R^8 are morpholin-4-yl.

In a particular group of compounds of the invention, R^1 is hydrogen or an alkyl group as defined in any one of paragraphs (9) to (12) above (particularly methyl) and ring A, R^3, n, and R^4 have any one of the definitions set out herein.

In a further particular group of compounds of the invention, R^1 is an alkyl group as defined in any one of paragraphs (14) to (16) above, particularly a methyl group, and ring A, R^3, n, and R^4 have any one of the definitions set out herein.

In a further group of compounds of the invention, R^4 is a sub-group of formula (iiib) as defined in any one of paragraphs (29) to (34) above, and particularly a sub-group of formula (iiib) as defined in any one of paragraphs (33) to (34) above, and ring A, R^1, R^3, and n have any one of the definitions set out herein.

In a further group of compounds of the invention:

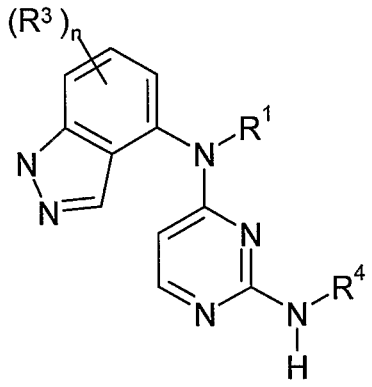
R^1 is an alkyl group as defined in any one of paragraphs (14) to (16) above, particularly a methyl group,

R^4 is a sub-group of formula (iiib) as defined in any one of paragraphs (29) to (34) above, and particularly a sub-group of formula (iiib) as defined in any one of paragraphs (33) to (34) above,

and ring A, R^1, R^3, and n have any one of the definitions set out herein.

The compounds of formula I described the first aspect of the invention above are all subject to the proviso that if Ring A, together with the phenyl ring to which it is attached, form an indazol-4-yl group, then R^1 is not hydrogen. Suitably, the compounds of formula (I) defined in the second aspect of the invention are also subject to this proviso.

This proviso excludes compounds of the structural formula shown below:



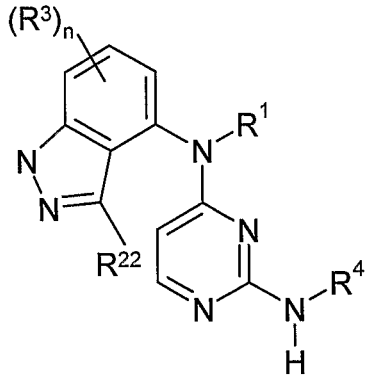
in which R^1 is hydrogen.

A particular group of compounds of formula I are subject to the proviso that if Ring A, together with the phenyl ring to which it is attached, form an indazol-4-yl group, then R^1 is a C_{1-6}alkyl group, particularly a C_{1-2}alkyl group, and most particularly methyl.

A further group of compounds of formula I are subject to the proviso that, if Ring A together with the phenyl ring to which it is attached, form an indazolyl group, then R^1 is a C_{1-6}alkyl group, particularly a C_{1-2}alkyl group and most particularly methyl.

A particular group of compounds of formula I are subject to the proviso that, if Ring A, together with the phenyl ring to which it is attached, form an indazol-4-yl group, then R^1 is a C_{1-6}alkyl group, particularly a C_{1-2}alkyl group, and most particularly methyl, and R^4 is a sub-group of formula (iiib) as defined in any one of paragraphs (29) to (34) above, and in particular a sub-group of formula (iiib) as defined in any one of paragraphs (33) to (34) above.

A particular group of compounds of the invention have the general structural formula (ID) shown below



(ID)

wherein R^1 is a C_{1-6}alkyl group, which is optionally substituted with one or more substituents selected from cyano, $-OR^2$, $-NR^{2a}R^{2b}$, where R^2, R^{2a} and R^{2b} are selected from hydrogen or C_{1-2}alkyl;

and R^3, n, R^{22}, and R^4 have any one of the definitions set out herein.

In a particular group of compound of formula (ID),

- R^1 is as defined in any one of paragraphs (14) to (16) above,
- R^{22} is as defined in any one of paragraphs (1) to (8) above,
- R^3, if present, is as defined in any one of paragraphs (21) to (25) above,
- n is as defined in any one of paragraphs (17) to (20) above, and
- R^4 is as defined in any one of paragraphs (26) to (34) above.

In compounds of formula (ID), R^1 is suitably an alkyl group as defined in any one of paragraphs (14) to (16) above. In particular compounds of formula (ID), R^1 is methyl.

In compounds of formula (ID), n is suitably 0 or 1, particularly 0.

In compounds of formula (ID), R^{22} is suitably hydrogen, halo, or C_{1-2}alkyl, and is especially hydrogen, methyl or chloro.

In compounds of formula (ID), R^4 is suitably a phenyl group as defined in any one of paragraphs (26) to (34) above, and particularly a phenyl group as defined in any one of paragraphs (29) to (34) above, and most particularly a phenyl group as defined in either of paragraphs (33) or (34) above.

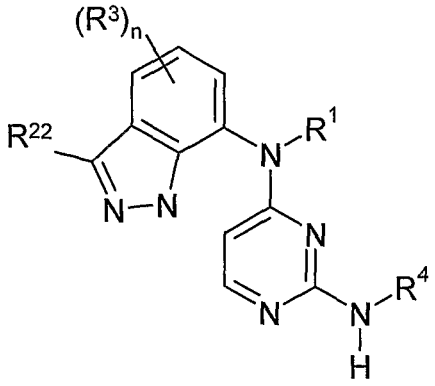
In a particular sub-group of compounds of formula (ID):

- R^1 is an alkyl group as defined in any one of paragraphs (14) to (16) above;
- n is 0;
- R^{22} is hydrogen, halo, or C_{1-2}alkyl; and
- R^4 is a phenyl group as defined in any one of paragraphs (29) to (34) above.

In a more particular sub-group of compounds of formula (ID):

- R^1 is methyl;
- n is 0;
- R^{22} is hydrogen, methyl or chloro; and
- R^4 is a phenyl group as defined in either of paragraphs (33) or (34) above.

A further particular group of compounds of the invention have the general structural formula (IE) shown below



(IE)

wherein R^1, R^{22}, R^3, n, and R^4 have any of the definitions set out herein.

In a particular group of compound of formula (IE),

- R^1 is as defined in any one of paragraphs (9) to (16) above,
- R^{22} is as defined in any one of paragraphs (1) to (8) above,
- R^3, if present, is as defined in any one of paragraphs (21) to (25) above,
- n is as defined in any one of paragraphs (17) to (20) above, and
- R^4 is as defined in any one of paragraphs (26) to (34) above.

In compounds of formula (IE), R^1 is suitably hydrogen or C_{1-2}alkyl, particularly methyl. In a particular group of compounds of formula (IE), R^1 is methyl.

In compounds of formula (IE), n is suitably 0 or 1, particularly 0.

In compounds of formula (IE), R^{22} is suitably hydrogen, halo, or C_{1-2}alkyl, and is especially hydrogen, methyl or chloro.

In compounds of formula (IE), R^4 is suitably a phenyl group as defined in any one of paragraphs (26) to (34) above, and particularly a phenyl group as defined in any one of paragraphs (29) to (34) above, and most particularly a phenyl group as defined in either of paragraphs (33) or (34) above.

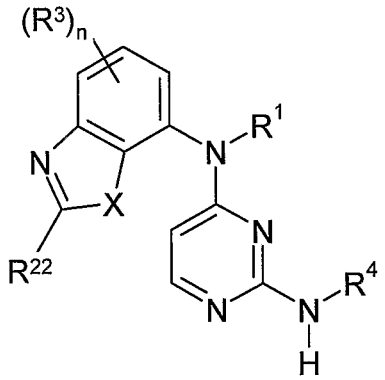
In a particular sub-group of compounds of formula (IE):

- R^1 is hydrogen or an alkyl group as defined in any one of paragraphs (14) to (16) above;
- n is 0;
- R^{22} is hydrogen, halo, or C_{1-2}alkyl; and
- R^4 is a phenyl group as defined in any one of paragraphs (29) to (34) above.

In a more particular sub-group of compounds of formula (IE):

- R^1 is methyl;
- n is 0;
- R^{22} is hydrogen, methyl or chloro; and
- R^4 is a phenyl group as defined in either of paragraphs (33) or (34) above.

A further particular group of compounds of the invention have the general structural formula (IF) shown below



(IF)

wherein R^1, R^{22}, R^3, n, and R^4 have any of the definitions set out herein.

In a particular group of compound of formula (IF),

- R^1 is as defined in any one of paragraphs (9) to (16) above,
- R^{22} is as defined in any one of paragraphs (1) to (8) above,
- R^3, if present, is as defined in any one of paragraphs (21) to (25) above,

- n is as defined in any one of paragraphs (17) to (20) above, and
- R^4 is as defined in any one of paragraphs (26) to (34) above.

In compounds of formula (IF), R^1 is suitably hydrogen or C_{1-2}alkyl, particularly methyl. In a particular group of compounds of formula (IE), R^1 is methyl.

In compounds of formula (IF), n is suitably 0 or 1, particularly 0.

In compounds of formula (IF), R^{22} is suitably hydrogen, halo, or C_{1-2}alkyl, and is especially hydrogen, methyl or chloro.

In compounds of formula (IF), R^4 is suitably a phenyl group as defined in any one of paragraphs (26) to (34) above, and particularly a phenyl group as defined in any one of paragraphs (29) to (34) above, and most particularly a phenyl group as defined in either of paragraphs (33) or (34) above.

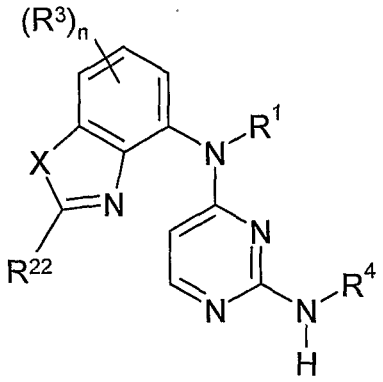
In a particular sub-group of compounds of formula (IF):

- R^1 is hydrogen or an alkyl group as defined in any one of paragraphs (14) to (16) above;
- n is 0;
- R^{22} is hydrogen, halo, or C_{1-2}alkyl; and
- R^4 is a phenyl group as defined in any one of paragraphs (29) to (34) above.

In a more particular sub-group of compounds of formula (IF):

- R^1 is methyl;
- n is 0;
- R^{22} is hydrogen, methyl or chloro; and
- R^4 is a phenyl group as defined in either of paragraphs (33) or (34) above.

A further particular group of compounds of the invention have the general structural formula (IG) shown below



(IG)

wherein R^1, R^{22}, R^3, n, and R^4 have any of the definitions set out herein.

In a particular group of compound of formula (IG),

- R^1 is as defined in any one of paragraphs (9) to (16) above,
- R^{22} is as defined in any one of paragraphs (1) to (8) above,
- R^3, if present, is as defined in any one of paragraphs (21) to (25) above,
- n is as defined in any one of paragraphs (17) to (20) above, and
- R^4 is as defined in any one of paragraphs (26) to (34) above.

In compounds of formula (IG), R^1 is suitably hydrogen or C_{1-2}alkyl, particularly methyl. In a particular group of compounds of formula (IE), R^1 is methyl.

In compounds of formula (IG), n is suitably 0 or 1, particularly 0.

In compounds of formula (IG), R^{22} is suitably hydrogen, halo, or C_{1-2}alkyl, and is especially hydrogen, methyl or chloro.

In compounds of formula (IG), R^4 is suitably a phenyl group as defined in any one of paragraphs (26) to (34) above, and particularly a phenyl group as defined in any one of paragraphs (29) to (34) above, and most particularly a phenyl group as defined in either of paragraphs (33) or (34) above.

In a particular sub-group of compounds of formula (IG):

- R^1 is hydrogen or an alkyl group as defined in any one of paragraphs (14) to (16) above;
- n is 0;
- R^{22} is hydrogen, halo, or C_{1-2}alkyl; and
- R^4 is a phenyl group as defined in any one of paragraphs (29) to (34) above.

In a more particular sub-group of compounds of formula (IG):

- R^1 is methyl;
- n is 0;
- R^{22} is hydrogen, methyl or chloro; and
- R^4 is a phenyl group as defined in either of paragraphs (33) or (34) above.

Particular compounds of the invention include any one of the following:

N~4~-(5-Chloro-1,3-benzodioxol-4-yl)-N~2~-(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(2-chlorophenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-1H-indazol-6-ylpyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-phenylpyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(2-fluorophenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(3-fluorophenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(4-fluorophenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(3-ethynylphenyl)pyrimidine-2,4-diamine;

3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzonitrile;

4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzonitrile;

[3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)phenyl]methanol;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(4-methoxyphenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(3-chlorophenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(4-chlorophenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(2,4-difluorophenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(3,5-difluorophenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-1H-indol-5-ylpyrimidine-2,4-diamine;
[4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)phenyl]acetonitrile;
N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-1H-indol-4-ylpyrimidine-2,4-diamine;
3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzamide;
4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzamide;
N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-1H-indol-6-ylpyrimidine-2,4-diamine;
3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-(2-methoxyethyl)benzamide;
N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-[4-(pyridin-2-ylmethoxy)phenyl]pyrimidine-2,4-diamine;
1-[4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)phenyl]-N-methylmethanesulfonamide;
N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-[3-(2-pyrrolidin-1-ylethoxy)phenyl]pyrimidine-2,4-diamine;
N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(3-chloro-4-morpholin-4-ylphenyl)pyrimidine-2,4-diamine;
N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-[4-(2-morpholin-4-ylethoxy)phenyl]pyrimidine-2,4-diamine;
4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-(2-hydroxyethyl)-N-methylbenzenesulfonamide;
4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-[2-(diethylamino)ethyl]benzamide;
N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-{4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}pyrimidine-2,4-diamine;
N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-{4-[(3-fluorobenzyl)oxy]-3-methoxyphenyl}pyrimidine-2,4-diamine;
N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-{4-[(2-fluorobenzyl)oxy]-3-methoxyphenyl}pyrimidine-2,4-diamine;
4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-(2-methoxyethyl)benzenesulfonamide;
N-[4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)phenyl]-N-methylacetamide;

N-[5-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-2-methylphenyl]acetamide;

N-[4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzyl]acetamide;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-[3-(methylsulfonyl)phenyl]pyrimidine-2,4-diamine;

4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzenesulfonamide;

3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzenesulfonamide;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-[4-(trifluoromethoxy)phenyl]pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(4-morpholin-4-ylphenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(2-morpholin-4-ylphenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(3-morpholin-4-ylphenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-[4-(2-ethoxyethoxy)phenyl]pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(2,3,4-trimethoxyphenyl)pyrimidine-2,4-diamine;

N-[3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)phenyl]methanesulfonamide;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-[3-(dimethylamino)phenyl]pyrimidine-2,4-diamine;

2-[4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)phenyl]ethanol;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(3-chloro-4-fluorophenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(4-chloro-2-fluorophenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(3-chloro-2-fluorophenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(5-chloro-2-fluorophenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(4-chloro-3-fluorophenyl)pyrimidine-2,4-diamine;

5-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-1,3-dihydro-2H-indol-2-one;

N-[4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)phenyl]acetamide;

3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-methylbenzamide;

4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-methylbenzamide;

N~2~-1,3-benzothiazol-6-yl-N~4~-(5-chloro-1,3-benzodioxol-4-yl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(2,5-dimethoxyphenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(2,4-dimethoxyphenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(3,5-dimethoxyphenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(3,4-dimethoxyphenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(5-chloro-2-methoxyphenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(2-chloro-5-methoxyphenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(3-chloro-2-methoxyphenyl)pyrimidine-2,4-diamine;

N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-[3-(1,3-oxazol-5-yl)phenyl]pyrimidine-2,4-diamine;

N~4~-(1*H*-Indazol-7-yl)-N~2~-(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine;

N'-(1-methylindol-4-yl)-N-(3,4,5-trimethoxyphenyl)-pyrimidine-2,4-diamine ;

N'-(5-bromobenzo[1,3]dioxol-4-yl)-N-(3,4,5-trimethoxyphenyl)-pyrimidine-2,4-diamine;

N'-benzo[1,3]dioxol-4-yl-N-(3,4,5-trimethoxyphenyl)-pyrimidine-2,4-diamine;

N'-(5-fluorobenzo[1,3]dioxol-4-yl)-N-(3,4,5-trimethoxyphenyl)-pyrimidine-2,4-diamine;

N'-(2,2-difluorobenzo[1,3]dioxol-4-yl)-N-(3,4,5-trimethoxyphenyl)-pyrimidine-2,4-diamine;

1-[7-[2-(3,4,5-trimethoxyphenyl)aminopyrimidin-4-yl]amino-2,3-dihydroindol-1-yl]ethanone; N'-(1H-indol-4-yl)-N-(3,4,5-trimethoxyphenyl)-pyrimidine-2,4-diamine;

N'-(6-chlorobenzofuran-7-yl)-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine;

N'-(2,3-dihydrobenzofuran-7-yl)-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine;

N'-(benzofuran-7-yl)-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine;

N'-(1H-benzotriazol-4-yl)-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine;

N'-(3-chloro-1H-indol-7-yl)-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine;

N'-(6-methoxybenzo[1,3]dioxol-4-yl)-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine;

4-[[2-[(3-methylsulfonylphenyl)amino]pyrimidin-4-yl]amino]benzo[1,3]dioxole-5-carboxamide;

N'-isoquinolin-5-yl-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine;

N'-benzooxazol-7-yl-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine;

N'-benzooxazol-4-yl-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine;

3-[4-(1H-indazol-4-yl-methyl-amino)pyrimidin-2-yl]-N,N-dimethyl-benzamide;

N-methyl-N-[2-(3-methylsulfonylphenyl)pyrimidin-4-yl]-1H-indazol-4-amine;

3-[4-(1H-indazol-4-yl-methyl-amino)pyrimidin-2-yl] benzenesulfonamide;

[3-[4-(1H-indazol-4-yl-methyl-amino)pyrimidin-2-yl]phenyl]methanol;

N-[3-[4-(1H-indazol-4-yl-methyl-amino)pyrimidin-2-yl]phenyl] methanesulfonamide

N-(3,5-dimorpholinophenyl)-N'-(1H-indazol-4-yl)-N'-methyl-pyrimidine-2,4-diamine;

[4-[[2-[(3,5-dimorpholin-4-ylphenyl)amino]pyrimidin-4-yl]amino]-1H-indazol-6-yl]methanol;

N-(3,5-dimorpholinophenyl)-N'-(3-methyl-1H-indazol-4-yl)pyrimidine-2,4-diamine;

N'-benzooxazol-7-yl-N-(3,5-dimorpholin-4-ylphenyl)pyrimidine-2,4-diamine;

N'-benzooxazol-7-yl-N-(3,5-dimorpholinophenyl)-N'-methyl-pyrimidine-2,4-diamine;

N-(3,5-dimorpholin-4-ylphenyl)-N'-methyl-N'-(3-methyl-1H-indazol-4-yl)pyrimidine-2,4-diamine;

N'-methyl-N'-(3-methyl-1H-indazol-4-yl)-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine;

N-(3,5-dimorpholin-4-ylphenyl)-N'-quinolin-5-yl-pyrimidine-2,4-diamine;

N'-(2,2-difluorobenzo[1,3]dioxol-4-yl)-N-(3,5-dimorpholin-4-ylphenyl)pyrimidine-2,4-diamine;

N-(3,5-dimorpholin-4-ylphenyl)-N'-(1H-indol-4-yl)pyrimidine-2,4-diamine;

N-(3,5-dimorpholin-4-ylphenyl)-N'-(2,5-dioxabicyclo[4.4.0]deca-6,8,10-trien-10-yl)pyrimidine-2,4-diamine;

N'-(1H-benzotriazol-4-yl)-N-(3,5-dimorpholin-4-ylphenyl)pyrimidine-2,4-diamine;

N'-(3-chloro-1H-indol-7-yl)-N-(3,5-dimorpholin-4-ylphenyl)pyrimidine-2,4-diamine;
N-(3,5-dimorpholin-4-ylphenyl)-N'-(1H-indazol-7-yl)pyrimidine-2,4-diamine;
or a pharmaceutically acceptable salt thereof.

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

cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

The compounds of the invention may be administered in the form of a pro-drug that is a compound that is broken down in the human or animal body to release a compound of the invention. A pro-drug may be used to alter the physical properties and/or the pharmacokinetic properties of a compound of the invention. A pro-drug can be formed when the compound of the invention contains a suitable group or substituent to which a property-modifying group can be attached. Examples of pro-drugs include *in vivo* cleavable ester derivatives that may be formed at a carboxy group or a hydroxy group in a compound of the Formula (I) and

in vivo cleavable amide derivatives that may be formed at a carboxy group or an amino group in a compound of the Formula (I).

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

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

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

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

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

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

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

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

f) N. Kakeya, *et al.*, Chem. Pharm. Bull., 32, 692 (1984);

g) T. Higuchi and V. Stella, "Pro-Drugs as Novel Delivery Systems", A.C.S. Symposium Series, Volume 14; and

h) E. Roche (editor), "Bioreversible Carriers in Drug Design", Pergamon Press, 1987.

A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula (I) that possesses a carboxy group is, for example, an *in vivo* cleavable ester thereof. An *in vivo* cleavable ester of a compound of the Formula (I) containing a carboxy group is, for example, a pharmaceutically-acceptable ester, which is cleaved in the human or animal body to produce the parent acid. Suitable pharmaceutically-acceptable esters for carboxy include (1-6C)alkyl esters such as methyl, ethyl and *tert*-butyl, (1-6C)alkoxymethyl esters such as methoxymethyl esters, (1-6C)alkanoyloxymethyl esters such as pivaloyloxymethyl esters, 3-phthalidyl esters, (3-8C)cycloalkylcarbonyloxy-(1-6C)alkyl esters such as cyclopentylcarbonyloxymethyl and 1-cyclohexylcarbonyloxyethyl esters, 2-oxo-1,3-dioxolenylmethyl esters such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl esters and (1-6C)alkoxycarbonyloxy-(1-6C)alkyl esters such as methoxycarbonyloxymethyl and 1-methoxycarbonyloxyethyl esters.

A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula (I) that possesses a hydroxy group is, for example, an *in vivo* cleavable ester or ether thereof. An *in vivo* cleavable ester or ether of a compound of the Formula (I) containing a hydroxy group is, for example, a pharmaceutically-acceptable ester or ether, which is cleaved in the human or animal body to produce the parent hydroxy compound. Suitable pharmaceutically-acceptable ester forming groups for a hydroxy group include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters). Further suitable pharmaceutically-acceptable ester forming groups for a hydroxy group include (1-10C)alkanoyl groups such as acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups, (1-10C)alkoxycarbonyl groups such as ethoxycarbonyl, *N*,*N*-[di-(1-4C)alkyl]carbamoyl, 2-dialkylaminoacetyl and 2-carboxyacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, *N*-alkylaminomethyl, *N*,*N*-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(1-4C)alkylpiperazin-1-ylmethyl. Suitable pharmaceutically-acceptable ether forming

groups for a hydroxy group include α-acyloxyalkyl groups such as acetoxymethyl and pivaloyloxymethyl groups.

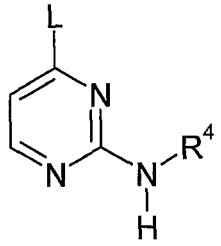
A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula (I) that possesses an amino group is, for example, an *in vivo* cleavable amide derivative thereof. Suitable pharmaceutically-acceptable amides from an amino group include, for example an amide formed with (1-10C)alkanoyl groups such as an acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, *N*-alkylaminomethyl, *N*,*N*-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(1-4C)alkylpiperazin-1-ylmethyl.

The *in vivo* effects of a compound of the Formula (I) may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of the Formula (I). As stated hereinbefore, the *in vivo* effects of a compound of the Formula (I) may also be exerted by way of metabolism of a precursor compound (a pro-drug).

Preparation of Compounds of Formula I

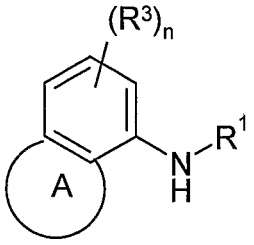
The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form.

Compounds of formula (I) can be prepared by various conventional methods as would be apparent to a chemist. In particular, compounds of formula (I) may be prepared by reacting a compound of formula (II):



(II)

where R^4 is as defined in relation to formula (I) provided that any functional groups are optionally protected, and L is a leaving group, with a compound of formula (III)

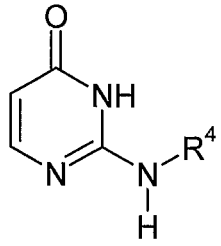


(III)

where A, R^1, R^3 and n are as defined in relation to formula (I) provided that any functional groups are optionally protected. Thereafter, any protecting groups can be removed using conventional methods, and if required, the compound of formula (I) can be converted to a different compound of formula (I) or a salt, again using conventional chemical methods.

Suitable leaving groups L are halo such as chloro. The reaction is suitably carried out in an organic solvent such as a C_{1-6}alkanol, for instance, n-butanol, dimethylamine (DMA), or N-methylpyrrolidine (NMP) or mixtures thereof. An acid, in particular, and inorganic acid such as hydrochloric acid is suitably added to the reaction mixture. The reaction is suitably conducted at elevated temperatures for example at from 80-150°C, conveniently at the reflux temperature of the solvent.

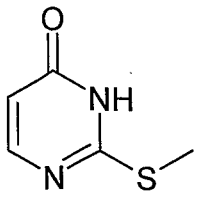
Compounds of formula (II) may be prepared by various methods including for example, where L is a halogen, by reacting a compound of formula (IV)



(IV)

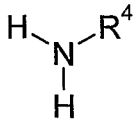
where R^4 is as defined in relation to formula (I), with a halogenating agent such as phosphorus oxychloride. The reaction is conducted under reactions conditions appropriate to the halogenating agent employed. For instance, it may be conducted at elevated temperatures, for example of from 50-100°C, in an organic solvent such as acetonitrile or dichloromethane (DCM).

Compounds of formula (IV) are suitably prepared by reacting a compound of formula (V)



(V)

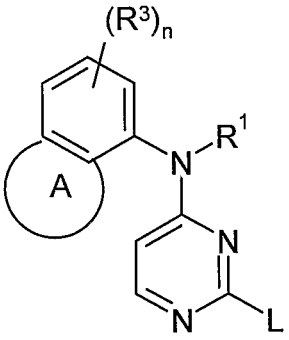
with a compound of formula (VI)



(VI)

where R^4 is as defined in relation to formula (I). The reaction is suitably effected in an organic solvent such as diglyme, again at elevated temperatures, for example of from 120-180°C, and conveniently at the reflux temperature of the solvent.

Alternatively, compounds of formula (I) may be prepared by reaction a compound of formula (VII)

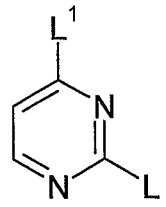


(VII)

where A, R^3 R^1 and n are as defined in relation to formula (I) provided that any functional groups can be optionally protected, and L is a leaving group as defined in relation to formula (II), with a compound of formula (VI) as defined above. Again, any protecting groups can be removed using conventional methods, and if required, the compound of formula (I) can be converted to a different compound of formula (I) or a salt, again using conventional chemical methods.

Conditions for carrying out such a reaction are broadly similar to those required for the reaction between compounds (II) and (III).

Compounds of formula (VII) are suitably prepared by reacting a compound of formula (III) as defined above with a compound of formula (VIII)



(VIII)

where L and L^1 are leaving groups such as halogen, and in particular chloro. The reaction is suitably effected in the presence of a strong base such as sodium hydride, in an organic solvent such as DMA. Depressed temperatures, for example from -20°C to 20°C, conveniently at about 0°C are suitably employed.

Compounds of formula (III) are either known compounds or they can be prepared from known compounds using analogous methods, which would be apparent to the skilled chemist. For instance, examples of compounds of formula (III) and their preparation are described in WO2001094341.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be

removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

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

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

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

Compounds of the formula I can be converted into further compounds of the formula I using standard procedures conventional in the art.

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

Particular examples of aromatic substitution reactions include the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halo group. Particular examples of nucleophilic substitution reactions include the introduction of an alkoxy group or of a monoalkylamino group, a dialkyamino group or a N-containing heterocycle using standard conditions. Particular examples of reduction reactions include the reduction of a carbonyl group to a hydroxy group with sodium borohydride or of a nitro group to an amino group by catalytic hydrogenation with a nickel catalyst or by treatment with iron in the presence of hydrochloric acid with heating.

The preparation of particular compounds of formula (I), such as compounds of formula (IA), (IB), (IC), (ID), (IE), (IF), and (IG), using the above-described methods form a further aspect of the invention.

According to a further aspect of the invention there is provided a pharmaceutical composition, which comprises a compound of the formula (I) and in particular a compound of formula (IA), (IB), (IC), (ID), (IE), (IF), and (IG), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compound of formula **(I)** will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg/m^2 body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the practitioner who is treating any particular patient may determine the optimum dosage.

Biological Assays

A) In vitro EphB4 enzyme assay

This assay detects inhibitors of EphB4-mediated phosphorylation of a polypeptide substrate using Alphascreen™ luminescence detection technology. Briefly, recombinant EphB4 was incubated with a biotinylated-polypeptide substrate (biotin-poly-GAT) in presence of magnesium-ATP. The reaction was stopped by addition of EDTA, together with streptavidin-coated donor beads which bind the biotin-substrate containing any phosphorylated tyrosine residues. Anti-phosphotyrosine antibodies present on acceptor beads bind to phosphorylated substrate, thus bringing the donor & acceptor beads into close proximity. Subsequent excitation of the donor beads at 680nm generated singlet oxygen species that interact with a chemiluminescer on the acceptor beads, leading to light emission at 520-620nm. The signal intensity is directly proportional to the level of substrate phosphorylation and thus inhibition is measured by a decrease in signal.

Test compounds were prepared as 10mM stock solutions in DMSO (Sigma-Aldrich Company Ltd, Gillingham, Dorset SP8 4XT Catalogue No.154938) and serially diluted with 5% DMSO to give a range of test concentrations at 6x the required final concentration. A 2µl aliquot of each compound dilution was transferred to appropriate wells of low volume white 384-well assay plates (Greiner, Stroudwater Business Park, Stonehouse, Gloucestershire, GL10 3SX, Cat No. 784075) in duplicate. Each plate also contained control wells: maximum signal was created using wells containing 2µl of 5% DMSO, and minimum signal corresponding to 100% inhibition were created using wells containing 2µl of 0.5M EDTA (Sigma-Aldrich Company Ltd, Catalogue No. E7889).

For the assay, in addition to 2µl of compound or control, each well of the assay plate contained; 10µl of assay mix containing final buffer (10mM Tris, 100µM EGTA, 10mM magnesium acetate, 4µM ATP, 500µM DTT, 1mg/ml BSA), 0.25ng of recombinant active EphB4 (amino acids 563-987; Swiss-Prot Acc. No. P54760) (ProQinase GmbH, Breisacher Str. 117, D-79106 Freiburg, Germany, Catalogue No 0178-0000-3) and 5nM of the poly-GAT substrate (CisBio International, BP 84175, 30204 Bagnols/Cèze Cedex, France, Catalogue No. 61GATBLB). Assay plates were then incubated at room temperature for 1 hour. The reaction was then stopped by addition of 5µl/well stop buffer (10mM Tris, 495mM EDTA, 1mg/ml BSA) containing 0.25ng each of AlphaScreen anti-

phosphoTyrosine-100 acceptor beads and streptavidin–coated donor beads (Perkin Elmer, Catalogue No 6760620M). The plates were sealed under natural lighting conditions, wrapped in aluminium foil and incubated in the dark for a further 20 hours.

The resulting assay signal was determined on the Perkin Elmer EnVision plate reader. The minimum value was subtracted from all values, and the signal plotted against compound concentration to generate IC_{50} data.

B) In vitro EphB4 cell assay

This assay identifies inhibitors of cellular EphB4 by measuring a decrease in phosphorylation of EphB4 following treatment of cells with compound. The endpoint assay used a sandwich ELISA to detect EphB4 phosphorylation status. Briefly, Myc-tagged EphB4 from treated cell lysate was captured on the ELISA plate via an anti-c-Myc antibody. The phosphorylation status of captured EphB4 was then measured using a generic phosphotyrosine antibody conjugated to HRP via a colourimetric output catalysed by HRP, with level of EphB4 phosphorylation directly proportional to the colour intensity. Absorbance was measured spectrophotometrically at 450nm.

Full length human EphB4 (Swiss-Prot Acc. No. P54760) was cloned using standard techniques from cDNA prepared from HUVEC using RT-PCR. The cDNA fragment was then sub-cloned into a pcDNA3.1 expression vector containing a Myc-His epitope tag to generate full-length EphB4 containing a Myc-His tag at the C-terminus (Invitrogen Ltd. Paisley, UK). CHO-K1 cells (LGC Promochem, Teddington, Middlesex, UK, Catalogue No. CCL-61) were maintained in HAM's F12 medium (Sigma-Aldrich Company Ltd, Gillingham, Dorset SP8 4XT, Catalogue No. N4888) containing 10% heat-inactivated foetal calf serum (PAA lab GmbH, Pasching, Austria Catalogue No. PAA-A15-043) and 1% glutamax-1 (Invitrogen Ltd., Catalogue No. 35050-038) at 37°C with 5% CO_2. CHO-K1 cells were engineered to stably express the EphB4-Myc-His construct using standard stable transfection techniques, to generate cells hereafter termed EphB4-CHO.

For each assay, 10,000 EphB4-CHO cells were seeded into each well of Costar 96-well tissue-culture plate (Fisher Scientific UK, Loughborough, Leicestershire, UK., Catalogue No. 3598) and cultured overnight in full media. On day 2, the cells were incubated overnight in 90µl/ well of media containing 0.1% Hyclone stripped-serum (Fisher Scientific UK, Catalogue No. SH30068.02). Test compounds were prepared as

10mM stock solutions in DMSO (Sigma-Aldrich Company Ltd, Gillingham, Dorset SP8 4XT Catalogue No.154938) and serially diluted with serum-free media to give a range of test concentrations at 10x the required final concentration. A 10µl aliquot of each compound dilution was transferred to the cell plates in duplicate wells, and the cells incubated for 1 hour at 37°C. Each plate also contained control wells: a maximum signal was created using untreated cells, and minimum signal corresponding to 100% inhibition was created using wells containing a reference compound known to abolish EphB4 activity.

Recombinant ephrin-B2-Fc (R&D Systems, Abingdon Science Park, Abingdon, Oxon OX14 3NB UK, Catalogue No. 496-EB), a Fc-tagged form of the cognate ligand for EphB4, was pre-clustered at a concentration of 3µg/ml with 0.3µg/ml anti-human IgG, Fc fragment specific (Jackson ImmunoResearch Labs, Northfield Business Park, Soham, Cambridgeshire, UK CB7 5UE, Catalogue No. 109-005-008) in serum-free media for 30 minutes at 4°C with occasional mixing. Following compound treatment, cells were stimulated with clustered ephrin-B2 at a final concentration of 1µg/ml for 20 minutes at 37°C to induce EphB4 phosphorylation. Following stimulation, the medium was removed and the cells lysed in 100µl/well of lysis buffer (25mM Tris HCl, 3mM EDTA, 3mM EGTA, 50mM NaF, 2mM orthovanadate, 0.27M Sucrose, 10mM ß-glycerophosphate, 5mM sodium pyrophosphate, 2% Triton X-100, pH 7.4).

Each well of an ELISA Maxisorp 96-well plate (Nunc; Fisher Scientific UK, Loughborough, Leicestershire, UK., Catalogue No. 456537) was coated overnight at 4°C with 100µl of anti-c-Myc antibody in Phosphate Buffered Saline (10µg/ml; produced at AstraZeneca). Plates were washed twice with PBS containing 0.05% Tween-20 and blocked with 250µl/well 3% TopBlock (Fluka) (Sigma-Aldrich Company Ltd, Gillingham, Dorset SP8 4XT, Catalogue No. 37766) for a minimum of 2 hours at room temperature. Plates were washed twice with PBS/0.05% Tween-20 and incubated with 100µl/well cell lysate overnight at 4°C. ELISA plates were washed four times with PBS/0.05% Tween-20 and incubated for 1 hour at room temperature with 100µl/well HRP-conjugated 4G10 anti-phosphotyrosine antibody (Upstate, Dundee Technology Park, Dundee, UK, DD2 1SW, Catalogue No. 16-105) diluted 1:6000 in 3% Top Block. ELISA plates were washed four times with PBS/0.05% Tween-20 and developed with 100µl/well TMB substrate (Sigma-Aldrich Company Ltd, Catalogue No. T0440). The reaction was stopped after 15 minutes

with the addition of 25µl/well 2M sulphuric acid. The absorbances were determined at 450nm using the Tecan SpectraFluor Plus. The minimum value was subtracted from all values, and the signal plotted against compound concentration to generate IC_{50} data.

C) Src Assay

In Vitro Enzyme Assay

The ability of test compounds to inhibit the phosphorylation of a tyrosine containing polypeptide substrate by the enzyme c-Src kinase was assessed using a conventional ELISA assay with a colorimetric endpoint.

Each well of Matrix 384-well plates (Matrix, Brooke Park, Wilmslow, Cheshire, SK9 3LP, UK, Catalogue No. 4311) were coated overnight at 4°C with 40µl of 10ug/ml stock of synthetic polyamino acid pEAY substrate (Sigma-Aldrich Company Ltd, Gillingham, Dorset, SP8 4XT, UK, Catalogue No. P3899) in phosphate buffered saline (PBS). Immediately prior to the assay, the plates were washed with 100µl/well of PBS containing Tween-20 and then with 50mM HEPES pH7.4.

Test compounds were prepared as 10mM stock solutions in DMSO (Sigma-Aldrich Company Ltd, Gillingham, Dorset, SP8 4XT, UK, Catalogue No.154938) and serially diluted with 10% DMSO to give a range of test concentrations at 4x the required final concentration. A 10µl aliquot of each compound dilution was transferred to the appropriate ELISA wells in duplicate. Each plate also contained control wells: maximum signal was created using wells containing 10µl of 10% DMSO, and minimum signal corresponding to 100% inhibition were created using wells containing 10µl of 0.5M EDTA (Sigma-Aldrich Company Ltd, Catalogue No. E7889).

10µl of a solution containing 8.8µM ATP and 80mM MnCl2 was added to each well to give a final concentration of 2.2µM and 20mM respectively. The reaction was initiated by addition of 20µl/well of assay buffer (final concentration of 50mM HEPES, 0.1mM sodium orthovanadate, 0.01% BSA, 0.1mM DTT, 0.05% Triton X-100, pH 7.4) containing active human recombinant c-Src kinase (Upstate, Dundee Technology Park, Dundee, UK, DD2 1SW, Catalogue No 14-117). Plates were then incubated at room temperature for 20 minutes before the kinase reaction was stopped by addition of 20µl/well of 0.5M EDTA.

The plates were washed three times with 100µl/well of PBS-Tween20 and then 40µl of a PBS-Tween20 and 0.5% BSA solution containing 4G10-HRP anti-phosphotyrosine antibody (Upstate, Catalogue No 16-105) added to each well. The plates were incubated for 1 hour at room temperature before being washed three times with 100µl/well of PBS-Tween20. Plates were developed with 40µl/well TMB substrate solution in DMSO (Sigma-Aldrich Company Ltd, Catalogue No. T2885) for up to one hour at room temperature. The reaction was then stopped with the addition of 20µl/well 2M sulphuric acid and the absorbances determined at 450nm using a plate reading spectrophotometer. The minimum value was subtracted from all values, and the signal plotted against compound concentration to generate IC_{50} data.

Compounds of the invention were active in the above assays, for instance, generally showing IC_{50} values of less than 100µM in Assay A and Assay B. Preferred compounds of the invention generally showing IC_{50} values of less than 30µM in Assay A and Assay B. For instance, Compound 59 of the Examples showed an IC_{50} of 0.46µM in assay A, an IC_{50} of 1.25µM in assay B, an IC_{50} of 0.33µM in assay C. Further illustrative IC_{50} values obtained using Assay B for a selection of the compounds exemplified in the present application are shown in Table A below.

Table A – Mean IC_{50} values obtained using Assay B

Compound No.	Mean IC_{50} (µM)
219	0.14
227	0.19
241	0.13
258	1.08
293	0.23
309	2.53
318	0.05
326	0.51

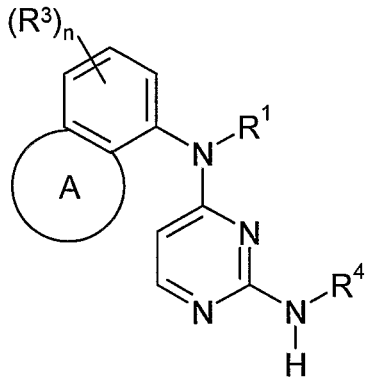
Compounds of the invention were also found active in a KinaseProfile™ assay for EphA2 kinase activity operated by Upstate of Charlotteville, VA 22903, USA. For instance, the compound of Example 1 above showed an IC_{50} of 15nM in this assay.

As a result of their activity in screens described above, the compounds of the present invention are expected to be useful in the treatment of diseases or medical

conditions mediated alone or in part by EphB4 enzyme activity, i.e. the compounds may be used to produce an EphB4 inhibitory effect in a warm-blooded animal in need of such treatment. Thus, the compounds of the present invention provide a method for treating the proliferation of malignant cells characterised by inhibition of the EphB4 enzyme, i.e. the compounds may be used to produce an anti-proliferative effect mediated alone or in part by the inhibition of EphB4.

In addition, certain compounds of the invention may also be active against the EphA2 or Src kinase enzymes, i.e. the compounds may also be used to produce an EphA2 and Src kinase inhibitory effect in a warm-blooded animal in need of such treatment. Thus, the compounds of the present invention provide a method for treating the proliferation of malignant cells characterised by inhibition of EphB4, EphA2 or Src enzymes, i.e. the compounds may be used to produce an anti-proliferative effect mediated alone or in part by the inhibition of EphB4, EphA2 or Src kinase.

According to a further aspect of the invention, there is provided the use of a compound of formula (IH)



(IH)

where $\mathbf{R^1}$ is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, or C_{2-6}alkynyl, wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by one or more substituent groups selected from cyano, nitro, $-OR^2$, $-NR^{2a}R^{2b}$, $-C(O)NR^{2a}R^{2b}$, or $-N(R^{2a})C(O)R^2$, halo or haloC_{1-4}alkyl, where R^2, R^{2a} and R^{2b} are selected from hydrogen or C_{1-6}alkyl such as methyl, or R^{2a} and R^{2b} together with the nitrogen atom to which they are attached may form a 5 or 6-membered heterocyclic ring, which optionally contains an additional heteroatom selected from N, O or S;

ring **A** is fused 5 or 6-membered carbocyclic or heterocyclic ring, which is saturated or unsaturated, and is optionally substituted on any available carbon atom by one or more substituent groups selected from halo, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, -$S(O)_z$-C_{1-6}alkyl (where z is 0, 1 or 2), or $-NR^aR^b$ (where R^a and R^b are each independently selected from hydrogen, C_{1-4}alkyl, or C_{1-4}alkylcarbonyl), and where any nitrogen atoms in the ring are optionally substituted by a C_{1-6}alkyl or C_{1-6}alkylcarbonyl;

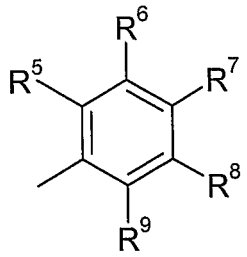
n is 0, 1, 2 or 3

and each group $\mathbf{R^3}$ is independently selected from halo, trifluoromethyl, cyano, nitro or a group of sub-formula (i) :

$$-X^1-R^{11} \qquad (i)$$

where $\mathbf{X^1}$ is selected from a direct bond or O, S, SO, SO_2, OSO_2, NR^{13}, CO, $CH(OR^{13})$, $CONR^{13}$, $N(R^{13})CO$, $SO_2N(R^{13})$, $N(R^{13})SO_2$, $C(R^{13})_2O$, $C(R^{13})_2S$, $C(R^{13})_2N(R^{13})$ and $N(R^{13})C(R^{13})_2$, wherein $\mathbf{R^{13}}$ is hydrogen or C_{1-6}alkyl and $\mathbf{R^{11}}$ is selected from hydrogen, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}cycloalkyl, aryl or heterocyclyl, C_{3-8}cycloalkylC_{1-6} alkyl, arylC_{1-6} alkyl or heterocyclylC_{1-6}alkyl, any of which may be optionally substituted with one or more groups selected from halo, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, C_{1-6}alkoxy, C_{2-6}alkenyoxyl, C_{2-6}alkynyloxy, C_{1-6}alkylthio, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, C_{1-6}alkylamino, di-(C_{1-6}alkyl)amino, C_{1-6}alkoxycarbonyl, N-C_{1-6}alkylcarbamoyl, N, N-di-(C_{1-6}alkyl)carbamoyl, C_{2-6}alkanoyl, C_{2-6}alkanoyloxy, C_{2-6}alkanoylamino, N-C_{1-6}alkyl-C_{2-6}alkanoylamino, C_{3-6}alkenoylamino, N-C_{1-6}alkyl-C_{3-6}alkenoylamino, C_{3-6}alkynoylamino, N-C_{1-6}alkyl- C_{3-6}alkynoylamino, N-C_{1-6}alkylsulphamoyl, N,N-di-(C_{1-6}alkyl)sulphamoyl, C_{1-6}alkanesulphonylamino and N-C_{1-6}alkyl-C_{1-6}alkanesulphonylamino, and any heterocyclyl group within R^{11} optionally bears 1 or 2 oxo or thioxo substituents; and

$\mathbf{R^4}$ is a group of sub-formula (iii)



(iii)

where $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$ and $\mathbf{R^9}$ are each independently selected from:

(i) hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl), heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) and wherein any aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl), heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) groups are optionally substituted on any available carbon atoms by halo, hydroxy, cyano, amino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino, and any nitrogen atoms present in a heterocyclyl group may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl, and where any sulphur atoms may be optionally oxidised to a sulphur oxide;

(ii) a group of sub-formula (iv):

$$-X^2-R^{14} \qquad \text{(iv)}$$

where $\mathbf{X^2}$ is selected from O, NR^{16}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{16})$, $CON(R^{16})$, $N(R^{16})CO$, $-N(R^{16})C(O)N(R^{16})-$, $-N(R^{16})C(O)O-$, $SON(R^{16})$, $N(R^{16})SO$, $SO_2N(R^{16})$, $N(R^{16})SO_2$, $C(R^{16})_2O$, $C(R^{16})_2S$ and $N(R^{16})C(R^{16})_2$, where each R^{16} is independently selected from hydrogen or C_{1-6}alkyl,

$\mathbf{R^{14}}$ is hydrogen, C_{1-6} alkyl, trifluoromethyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, or a 4- to 8-membered mono or bicyclic heterocyclyl ring (including 5 or 6 membered heteroaryl rings) or 4- to 8-membered mono or bicyclic heterocyclyl-C_{1-6}alkyl groups (including 5 or 6 membered heteroaryl-C_{1-6}alkyl groups) and wherein any aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl), heterocyclyl-C_{1-6}alkyl (including heteroaryl-

C_{1-6}alkyl) groups are optionally substituted on any available carbon atoms by oxo, halo, cyano, amino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino and any nitrogen atoms present in the heterocyclyl moieties may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl, and where any sulphur atoms may be optionally oxidised to a sulphur oxide;

iii) a group of sub-formula (v):

$$-X^3-R^{15}-Z \qquad (v)$$

where $\mathbf{X^3}$ is a direct bond or is selected from O, NR^{17}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{17})$, $CON(R^{17})$, $N(R^{17})CO$, $-N(R^{17})C(O)N(R^{17})-$, $-N(R^{17})C(O)O-$, $SO_2N(R^{17})$, $N(R^{17})SO_2$, $C(R^{17})_2O$, $C(R^{17})_2S$ and $N(R^{17})C(R^{17})_2$, where each R^{17} is independently selected from hydrogen or C_{1-6}alkyl;

$\mathbf{R^{15}}$ is a C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene, arylene, C_{3-12} carbocyclyl, heterocyclyl (including heteroaryl), any of which may be optionally substituted by one or more groups selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, amino, C_{1-6}alkylamino or di-(C_{1-6}alkyl)amino;

Z is halo, trifluoromethyl, cyano, nitro, aryl, C_{3-12} carbocyclyl or heterocyclyl (including heteroaryl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl and C_{1-6}alkoxy and wherein any heterocyclyl group within Z optionally bears 1 or 2 oxo substituents,

or Z is a group of sub-formula (vi)

$$-X^4-R^{18} \qquad (vi)$$

where $\mathbf{X^4}$ is selected from O, NR^{19}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{19})$, $CON(R^{19})$, $N(R^{19})CO$, $SO_2N(R^{19})$, $-N(R^{19})C(O)N(R^{19})-$, $-N(R^{19})C(O)O-$ $N(R^{19})SO_2$, $C(R^{19})_2O$, $C(R^{19})_2S$ and $N(R^{19})C(R^{19})_2$, where each R^{19} is independently selected from hydrogen or C_{1-6}alkyl; and R^{18} is selected from hydrogen, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl) or heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl and C_{1-6}alkoxy, and

wherein any heterocyclyl group within R^{18} optionally bears 1 or 2 oxo substituents; or

(iv) R^5 and R^6, R^6 and R^7, R^7 and R^8 or R^8 and R^9 are joined together to form a fused 5, 6 or 7-membered ring, wherein said ring is unsaturated or partially or fully saturated and is optionally substituted on any available carbon atom by halo, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, amino, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino, and said ring may contain one or more heteroatoms selected from oxygen, sulphur or nitrogen, where sulphur atoms may be optionally oxidised to a sulphur oxide, where any CH_2 groups may be substituted by a C(O) group, and where nitrogen atoms, depending upon valency considerations, may be substituted by a group R^{21}, where R^{21} is selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl;

or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for use in the treatment of cancer.

According to another aspect of the present invention there is provided a compound of the formula (I), (IA), (IB), (IC), (ID), (IE), (IF), (IG) or (IH), or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

Thus according to a further aspect of the invention there is provided a compound of the formula (I), (IA), (IB), (IC), (ID), (IE), (IF), (IG) or (IH), or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use as a medicament.

According to a further aspect of the invention there is provided a compound of the formula (I), (IA), (IB), (IC), (ID), (IE), (IF), (IG) or (IH), or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in the production of an EphB4 inhibitory effect in a warm blooded animal such as man.

According to a further aspect of the invention there is provided the use of a compound of the formula (I), (IA), (IB), (IC), (ID), (IE), (IF), (IG) or (IH), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an EphB4 inhibitory effect in a warm-blooded animal such as man.

According to a further aspect of the invention there is provided the use of a compound of the formula (I), (IA), (IB), (IC), (ID), (IE), (IF), (IG) or (IH), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a

medicament for use in the production of an EphB4, EphA2 and Src kinase inhibitory effect in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for producing an EphB4 inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the formula (I), (IA), (IB), (IC), (ID), (IE), (IF), (IG) or (IH), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

According to a further feature of this aspect of the invention there is provided a method for producing an EphB4, EphA2 and Src kinase inhibitory effect inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the formula (I), (IA), (IB), (IC), (ID), (IE), (IF), (IG) or (IH), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided a compound of the formula (I), (IA), (IB), (IC), (ID), (IE), (IF), (IG) or (IH), or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in the production of an anti-angiogenic effect in a warm-blooded animal such as man.

According to a further aspect of the invention there is provided the use of a compound of the formula (I), (IA), (IB), (IC), (ID), (IE), (IF), (IG) or (IH), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an anti-angiogenic effect in a warm-blooded animal such as man.

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

According to a further feature of the invention there is provided a compound of the formula (I), (IA), (IB), (IC), (ID), (IE), (IF), (IG) or (IH), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of cancer.

According to an additional feature of this aspect of the invention there is provided a compound of the formula (I), (IA), (IB), (IC), (ID), (IE), (IF), (IG) or (IH), or a pharmaceutically acceptable salt thereof, as defined hereinbefore, for use in the treatment of cancer.

According to an additional feature of this aspect of the invention there is provided a method of treating cancer in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the formula (I), (IA), (IB), (IC), (ID), (IE), (IF), (IG) or (IH), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

In a further aspect of the present invention there is provided the use of a compound of the formula (I), (IA), (IB), (IC), (ID), (IE), (IF), (IG) or (IH), or a pharmaceutically acceptable salt thereof, as defined hereinbefore, in the manufacture of a medicament for use in the treatment of solid tumour disease, in particular neuroblastomas, breast, liver, lung and colon cancer or leukemias.

In a further aspect of the present invention there is provided a method of treating neuroblastomas, breast, liver, lung and colon cancer or leukemias in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the formula (I), (IA), (IB), (IC), (ID), (IE), (IF), (IG) or (IH), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

The anti-cancer treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or radiotherapy or chemotherapy. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the anti-angiogenic treatment defined hereinbefore may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents:

(i) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan,

temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and polokinase inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

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

(iii) anti-invasion agents (for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341) and *N*-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; J. Med. Chem., 2004, 47, 6658-6661), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase);

(iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [Herceptin™], the anti-EGFR antibody panitumumab, the anti-erbB1 antibody cetuximab [Erbitux, C225] and any growth factor or growth factor receptor antibodies disclosed by Stern *et al.* Critical reviews in oncology/haematology, 2005, Vol. 54, pp11-29); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-

morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib, inhibitors of the hepatocyte growth factor family, inhibitors of the platelet-derived growth factor family such as imatinib, inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006)), inhibitors of cell signalling through MEK and/or AKT kinases, inhibitors of the hepatocyte growth factor family, c-kit inhibitors, abl kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti-vascular endothelial cell growth factor antibody bevacizumab (Avastin™) and VEGF receptor tyrosine kinase inhibitors such as 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474; Example 2 within WO 01/32651), 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), vatalanib (PTK787; WO 98/35985) and SU11248 (sunitinib; WO 01/60814), compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin)];

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

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

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

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines

such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

According to this aspect of the invention there is provided a pharmaceutical composition comprising a compound of the formula **(I)** as defined hereinbefore and an additional anti-tumour substance as defined hereinbefore for the conjoint treatment of cancer.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular cell-proliferation disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged.

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

The invention will now be illustrated in the following Examples in which, generally:

For examples 1 to 9

(i) operations were carried out at ambient temperature, *i.e.* in the range 17 to 25°C and under an atmosphere of an inert gas such as nitrogen or argon unless otherwise stated;

(ii) in general, the course of reactions was followed by thin layer chromatography (TLC) and/or analytical high pressure liquid chromatography (HPLC); the reaction times that are given are not necessarily the minimum attainable;

(iii) when necessary, organic solutions were dried over anhydrous magnesium sulphate, work-up procedures were carried out using traditional layer separating techniques or an ALLEXIS (MTM) automated liquid handler, evaporations were carried out either by rotary evaporation *in vacuo* or in a Genevac HT-4 / EZ-2.

(iv) yields, where present, are not necessarily the maximum attainable, and when necessary, reactions were repeated if a larger amount of the reaction product was required;

(v) in general, the structures of the end-products of the Formula I were confirmed by nuclear magnetic resonance (NMR) and/or mass spectral techniques; electrospray mass spectral data were obtained using a Waters ZMD or Waters ZQ LC/mass spectrometer acquiring both positive and negative ion data, generally, only ions relating to the parent structure are reported; proton NMR chemical shift values were measured on the delta scale using either a Bruker Spectrospin DPX300 spectrometer operating at a field strength of 300 MHz, a Bruker Dpx400 operating at 400MHz or a Bruker Advance operating at 500MHz. The following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad;

(vi) unless stated otherwise compounds containing an asymmetric carbon and/or sulphur atom were not resolved;

(vii) intermediates were not necessarily fully purified but their structures and purity were assessed by TLC, analytical HPLC, infra-red (IR) and/or NMR analysis;

(viii) unless otherwise stated, column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385);

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

(x) the following analytical HPLC methods were used; in general, reversed-phase silica was used with a flow rate of about 1 ml per minute and detection was by Electrospray Mass Spectrometry and by UV absorbance at a wavelength of 254 nm; for each method Solvent A was water and Solvent B was acetonitrile; the following columns and solvent mixtures were used :-

Preparative HPLC was performed on C18 reversed-phase silica, on a Phenomenex "Gemini" preparative reversed-phase column (5 microns silica, 110A, 21.1 mm diameter, 100 mm length) using decreasingly polar mixtures as eluent, for example decreasingly

polar mixtures of water (containing 0.1% formic acid or 0.1% ammonia) as solvent A and acetonitrile as solvent B; either of the following preparative HPLC methods were used:

Method A: a solvent gradient over 9.5 minutes, at 25mls per minute, from a 85:15 mixture of solvents A and B respectively to a 5:95 mixture of solvents A and B.

Method B: a solvent gradient over 9.5 minutes, at 25mls per minute, from a 60:40 mixture of solvents A and B respectively to a 5:95 mixture of solvents A and B.

(xi) where certain compounds were obtained as an acid-addition salt, for example a mono-hydrochloride salt or a di-hydrochloride salt, the stoichiometry of the salt was based on the number and nature of the basic groups in the compound, the exact stoichiometry of the salt was generally not determined, for example by means of elemental analysis data;

For examples 10 to 28

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

(ii) organic solutions were dried over anhydrous magnesium sulfate or anhydrous sodium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600 to 4000 Pascals; 4.5 to 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 / or analytical LC-MS, and reaction times are given for illustration only. The retention times (t_R) were measured on a LC/MS Waters 2790 / ZMD Micromass system equipped with a Waters Symmetry column (C18, 3.5μM, 4.6 x 50 mm); detection UV 254 nM and MS; elution: flow rate 2.5 ml/min, linear gradient from 95% water - 5% methanol containing 5% formic acid to 40% water - 55% acetonitrile - 5% methanol containing 5% formic acid over 3 minutes; then linear gradient to 95% acetonitrile - 5% methanol containing 5% formic acid over 1 minute;

(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 500 MHz using perdeuterio dimethyl sulfoxide (DMSO-d_6) as solvent unless otherwise indicated; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad;

(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 $(MH)^+$ which refers to the protonated mass ion; reference to M^+ is to the mass ion generated by loss of an electron; and reference to $M\text{-}H^+$ is to the mass ion generated by loss of a proton;

(xi) unless stated otherwise compounds containing an asymmetrically substituted carbon and/or sulfur atom have not been resolved;

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

(xiii) all microwave reactions were carried out in a Personal Chemistry EMRYS™ Optimizer EXP microwave synthesisor;

(xiv) preparative high performance liquid chromatography (HPLC) was performed on a Waters instrument using the following conditions:

Column:	30 mm x 15 cm Xterra Waters, C18, 5 mm
Solvent A:	Water with 1% acetic acid or 2 g/l ammonium carbonate
Solvent B:	Acetonitrile
Flow rate:	40 ml / min
Run time:	15 minutes with a 10 minute gradient from 5-95% B
Wavelength:	254 nm
Injection volume	2.0-4.0 ml;

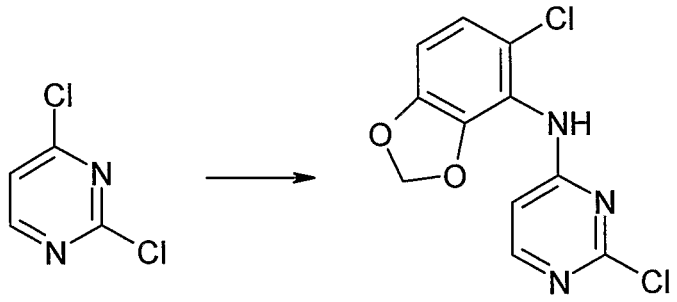
In addition, the following abbreviations have been used, where necessary:-

DMSO	dimethylsulphoxide
NMP	1-methyl-2-pyrrolidinone
DMA	N, N-dimethylacetamide
DCM	Dichloromethane
THF	tetrahydrofuran;
DMF	*N,N*-dimethylformamide;
DTAD	di-tert-butyl azodicarboxylate;
DIPEA	di-isopropylethylamine;
IPA	isopropyl alcohol;
Ether	diethyl ether; and
TFA	trifluoroacetic acid.

Example 1

Step 1

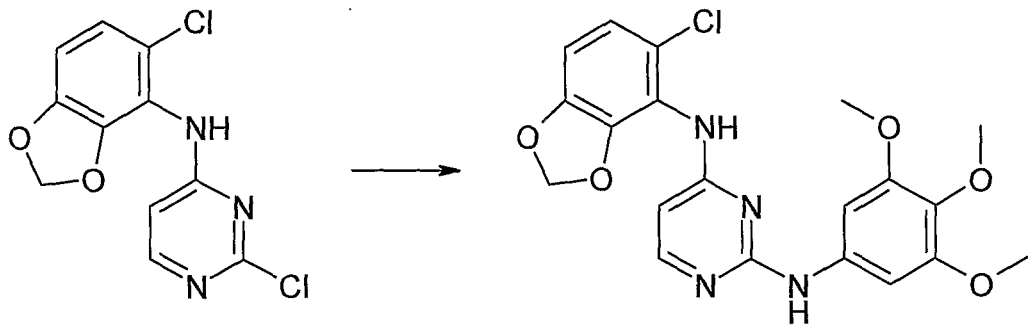
2-Chloro-*N*-(5-chloro-1,3-benzodioxol-4-yl)pyrimidin-4-amine



Sodium hydride (13.4 g, 60% dispersion in mineral oil) was added portion-wise to (5-chloro-1,3-benzodioxol-4-yl)amine (11.5 g, prepared as described in WO2001094341) in DMA (100 ml) at 0°C. 2, 4-Dichloropyrimidine (10 g) was added and the reaction warmed to room temperature and stirred overnight. The reaction was quenched cautiously with water, the solution filtered and concentrated and the residue dissolved in DCM, washed with water and brine, dried and concentrated to give the title compound as a dark brown oil that was used without further purification (16 g, 85%); NMR Spectrum (300 MHz, DMSO) 6.10 (s, 2H), 6.58 (d, 1H), 6.94 (d, 1H), 7.05 (d, 1H), 8.15 (d, 1H), 9.76 (s, 1H); Mass Spectrum M^+ 284.4.

Step 2

N~4~~-(5-Chloro-1,3-benzodioxol-4-yl)-N~2~~-(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine (Compound No. 1)



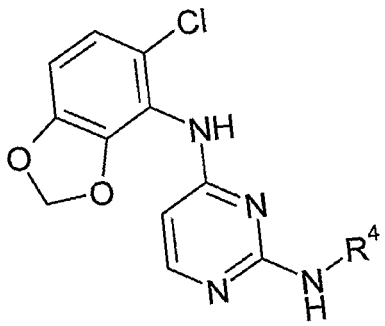
Compound 1

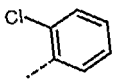
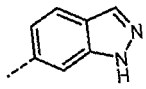
3, 4, 5-Trimethoxyaniline (103 mg) and 2-chloro-*N*-(5-chloro-1,3-benzodioxol-4-yl)pyrimidin-4-amine (200 mg) were dissolved in n-butanol (1 ml) and DMA (1 ml) and a solution of HCl in diethyl ether (0.7 ml, 1M) added. The reaction was heated at 120°C for 3 hours then cooled to room temperature and concentrated in vacuo. The residue was purified by reverse phase chromatography to give the title compound as a solid (69 mg, 23%); NMR Spectrum (300 MHz, DMSO) 3.58 (s, 9H), 5.98 (s, 2H), 8.85 (s, 1H), 6.10 (d, 1H), 6.87 (d, 1H), 7.02 (d, 1H), 7.05 (s, 2H), 7.99 (d, 1H); Mass Spectrum MH^+ 431.38.

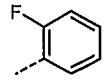
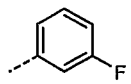
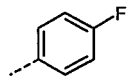
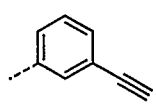
Example 2

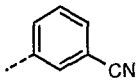
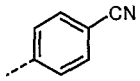
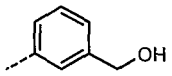
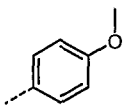
The procedure described above in Example 1 was repeated using the appropriate aniline (which were sourced commercially or prepared as described in the Method section below). Thus were obtained the compounds described below in **Table 1**.

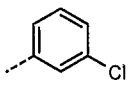
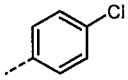
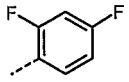
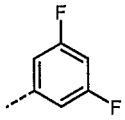
Table 1

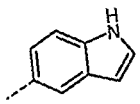
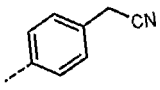
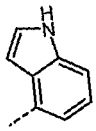
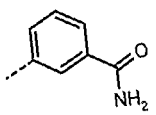


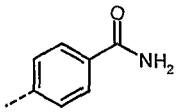
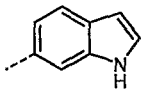
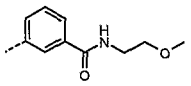
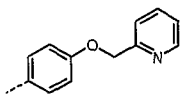
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
2	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(2-chlorophenyl) pyrimidine-2,4-diamine		375.52 (M+)		
3	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~1H-indazol-6-ylpyrimidine-2,4-diamine		381.57 (MH+)		
4	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~phenylpyrimidine-2,4-diamine		341.4 (MH+)	6.00 (s, 2H), 6.15 (d, 1H), 6.82 (t, 1H), 6.93 (d, 1H), 7.09 (m, 3H), 7.60 (d, 2H), 8.00 (d, 2H), 8.97 (s, 1H), 9.08 (s, 1H)	

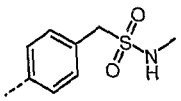
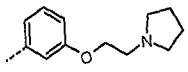
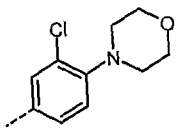
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
5	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(2-fluorophenyl)pyrimidine-2,4-diamine		359.39 (MH+)	6.00 (s, 2H), 6.14 (d, 1H), 6.91 (d, 1H), 6.98 (m, 2H), 7.04 (d, 1H), 7.13 (m, 1H), 7.86 (m, 1H), 7.99 (d, 1H), 8.30 (s, 1H), 9.00 (s, 1H)	
6	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(3-fluorophenyl) pyrimidine-2,4-diamine		359.4 (MH+)	6.03 (s, 2H), 6.20 (d, 1H), 6.61 (m, 1H), 6.92 (d, 1H), 7.05 (d, 1H), 7.12 (m, 1H), 7.32 (d, 1H), 7.64 (d, 1H), 8.03 (d, 1H), 9.07 (s, 1H), 9.33 (s, 1H)	
7	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(4-fluorophenyl) pyrimidine-2,4-diamine		359.4 (MH+)	6.03 (s, 2H), 6.16 (d, 1H), 6.94 (m, 3H), 7.07 (d, 1H), 7.61 (dd, 2H), 8.00 (d, 1H), 8.98 (s, 1H), 9.11 (s, 1H)	
8	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(3-ethynylphenyl) pyrimidine-2,4-diamine		365.42 (MH+)	4.03 (s, 1H), 6.02 (s, 2H), 6.19 (d, 1H), 6.94 (m, 2H), 7.08 (m, 2H), 7.68 (d, 1H), 7.76 (s, 1H), 8.03 (d, 1H), 9.02 (s, 1H), 9.21 (s, 1H)	

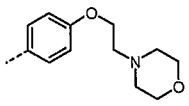
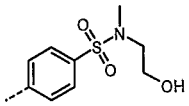
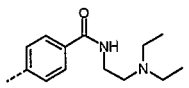
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
9	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino] pyrimidin-2-yl} amino) benzonitrile		366.42 (MH+)	6.04 (s, 2H), 6.23 (d, 1H), 6.92 (d, 1H), 7.08 (d, 1H), 7.70 (m, 2H), 7.86 (d, 1H), 8.09 (m, 2H), 9.13 (s, 1H), 9.50 (s, 1H)	
10	4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino) benzonitrile		366.42 (MH+)	6.04 (s, 2H), 6.28 (d, 1H), 6.99 (d, 1H), 7.09 (d, 1H), 7.52 (d, 2H), 7.72 (d, 2H), 8.09 (d, 1H), 9.19 (s, 1H), 9.70 (s, 1H)	
11	[3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino) phenyl] methanol		371.44 (MH+)	4.36 (d, 2H), 5.01 (t, 1H), 6.01 (s, 2H), 6.13 (d, 1H), 6.82 (d, 1H), 6.92 (d, 1H), 7.04 (m, 2H), 7.50 (m, 2H), 7.99 (d, 1H), 8.94 (s, 1H), 9.05 (s, 1H)	
12	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(4-methoxyphenyl)pyrimidine-2,4-diamine		371.45 (MH+)	3.70 (s, 3H), 6.01 (s, 2H), 6.09 (d, 1H), 6.70 (d, 2H), 6.93 (d, 1H), 7.04 (d, 1H), 7.50 (d, 2H), 7.95 (d, 1H), 8.86 (s, 1H), 8.90 (s, 1H)	

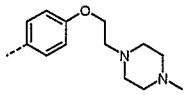
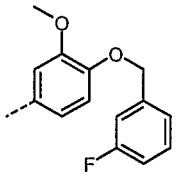
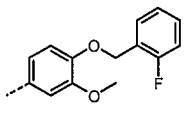
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
13	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(3-chlorophenyl) pyrimidine-2,4-diamine		375.4 (M+)	6.03 (s, 2H), 6.22 (d, 1H), 6.86 (dd, 1H), 7.92 (d, 1H), 7.06 (d, 1H), 7.13 (dd, 1H), 7.50 (d, 1H), 7.82 (m, 1H), 8.04 (d, 1H), 9.06 (s, 1H), 9.32 (s, 1H)	
14	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(4-chlorophenyl) pyrimidine-2,4-diamine		375.41 (M+)	6.04 (s, 2H), 6.19 (d, 1H), 6.97 (d, 1H), 7.09 (m, 3H), 7.64 (d, 2H), 8.03 (d, 1H), 9.04 (s, 1H), 9.27 (s, 1H)	
15	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(2,4-difluorophenyl)pyrimidine-2,4-diamine		377.42 (MH+)	6.06 (s, 2H), 6.16 (d, 1H), 7.91 (m, 2H), 7.08 (d, 1H), 7.22 (m, 1H), 7.78 (m, 1H), 8.00 (d, 1H), 8.46 (s, 1H), 8.98 (s, 1H)	
16	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(3,5-difluorophenyl) pyrimidine-2,4-diamine		377.42 (MH+)	6.03 (s, 2H), 6.26 (d, 1H), 6.58 (m, 1H), 6.92 (d, 1H), 7.05 (d, 1H), 7.87 (d, 2H), 8.06 (d, 1H), 9.15 (s, 1H), 9.55 (s, 1H)	

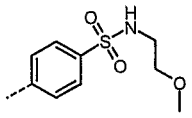
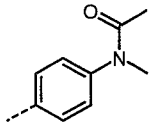
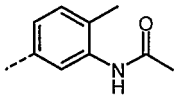
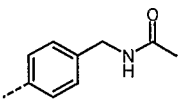
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
17	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-1H-indol-5-yl pyrimidine-2,4-diamine		380.44 (MH+)	6.01 (s, 2H), 6.10 (m, 1H), 6.20 (s, 1H), 6.96 (d, 1H), 7.07 (d, 1H), 7.17 (m, 3H), 7.90 (s, 1H), 7.97 (d, 1H), 8.81 (s, 1H), 8.87 (s, 1H), 10.78 (s, 1H)	
18	[4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino] pyrimidin-2-yl}amino)phenyl] acetonitrile		380.45 (MH+)	3.90 (s, 1H), 6.04 (s, 2H), 6.17 (d, 1H), 6.92 (d, 1H), 7.08 (m, 3H), 7.62 (d, 2H), 8.01 (d, 1H), 9.01 (s, 1H), 9.17 (s, 1H)	
19	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-1H-indol-4-yl pyrimidine-2,4-diamine		380.46 (MH+)	6.02 (s, 2H), 6.15 (d, 1H), 6.80 (m, 2H), 7.96 (m, 2H), 7.05 (d, 1H), 7.20 (m, 1H), 7.64 (d, 1H), 8.02 (d, 1H), 8.54 (s, 1H), 8.93 (s, 1H), 10.94 (s, 1H)	
20	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino] pyrimidin-2-yl}amino) benzamide		384.44 (MH+)	6.03 (s, 2H), 6.21 (d, 1H), 6.98 (d, 1H), 7.09 (d, 2H), 7.66 (m, 5H), 8.05 (d, 1H), 9.08 (s, 1H), 9.39 (s, 1H)	

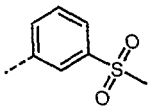
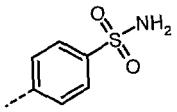
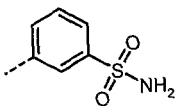
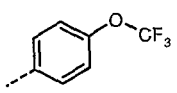
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
21	4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino] pyrimidin-2-yl}amino) benzamide		384.45 (MH+)	6.03 (s, 2H), 6.21 (d, 1H), 6.98 (d, 1H), 7.09 (d, 2H), 7.65 (m, 5H), 8.05 (d, 1H), 9.08 (s, 1H), 9.38 (s, 1H)	
22	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-1H-indol-6-ylpyrimidine-2,4-diamine		380.46 (MH+)		
23	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-(2-methoxyethyl) benzamide		442.45 (MH+)		
24	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-[4-(pyridin-2-ylmethoxy) phenyl] pyrimidine-2,4-diamine			5.19 (s, 2H), 6.03 (s, 2H), 6.17 (d, 1H), 6.90 (d, 1H), 7.00 (d, 1H), 7.16 (d, 1H), 7.37 (m, 1H), 7.43 (dd, 1H), 7.57 (d, 1H), 7.86 (m, 2H), 8.00 (d, 1H), 8.60 (d, 1H), 8.99 (s, 1H), 9.12 (s, 1H)	

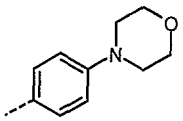
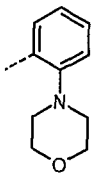
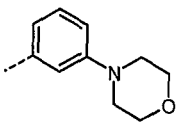
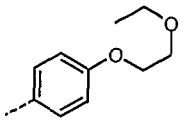
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
25	1-[4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino) phenyl]-N-methylmethane sulfonamide		448.39 (MH+)		
26	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-[3-(2-pyrrolidin-1-ylethoxy)phenyl] pyrimidine-2,4-diamine		454.47 (MH+)	1.70 (m, 4H), 2.53 (m, 4H, obscured by solvent), 2.77 (t, 2H), 3.95 (t, 2H), 6.02 (s, 2H), 6.15 (d, 1H), 6.43 (dd, 1H), 6.90 (d, 1H), 7.00 (t, 1H), 7.05 (d, 1H), 7.26 (m, 2H), 8.00 (d, 1H), 8.94 (s, 1H), 9.00 (s, 1H)	
27	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(3-chloro-4-morpholin-4-ylphenyl) pyrimidine-2,4-diamine		460.4 (M+)	2.88 (m, 4H), 3.74 (m, 4H), 6.00 (s, 2H), 6.16 (d, 1H), 6.94 (m, 3H), 7.04 (d, 1H), 7.45 (dd, 1H), 7.82 (d, 1H), 8.01 (d, 1H), 8.99 (s, 1H), 9.13 (s, 1H)	

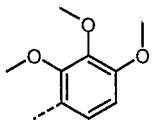
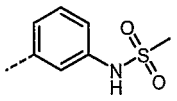
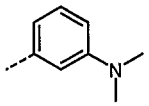
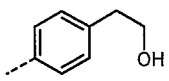
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
28	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-[4-(2-morpholin-4-ylethoxy) phenyl] pyrimidine-2,4-diamine		470.45 (MH+)	2.47 (m, 4H), 2.67 (t, 2H), 3.60 (m, 4H), 4.02 (t, 2H), 6.03 (s, 2H), 6.10 (d, 1H), 6.70 (d, 2H), 6.93 (d, 1H), 7.06 (d, 1H), 7.50 (d, 2H), 7.96 (d, 1H), 8.87 (s, 1H), 8.89 (s, 1H)	
29	4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino] pyrimidin-2-yl}amino)-N-(2-hydroxyethyl)-N-methyl benzene sulfonamide		478.45 (MH+)	2.68 (s, 3H), 2.95 (t, 2H), 3.53 (m, 2H), 4.74 (t, 1H), 6.04 (s, 2H), 6.26 (d, 1H), 6.97 (d, 1H), 7.08 (d, 1H), 7.47 (d, 2H), 7.83 (d, 2H), 8.07 (d, 1H), 9.15 (s, 1H), 9.65 (s, 1H)	
30	4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino] pyrimidin-2-yl}amino)-N-[2-(diethylamino) ethyl]benzamide		483.56 (MH+)	1.00 (t, 6H), 2.53 (m, 6H, obscured by solvent), 3.30 (m, 2H, obscured by water), 6.03 (s, 2H), 6.21 (d, 1H), 6.96 (d, 1H), 7.07 (d, 1H), 7.60 (d, 2H), 7.67 (d, 2H), 8.05 (m, 2H), 9.07 (s, 1H), 9.38 (s, 1H)	

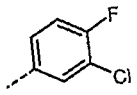
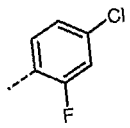
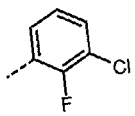
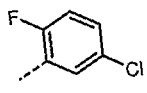
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
31	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-{4-[2-(4-methylpiperazin-1-yl)ethoxy] phenyl} pyrimidine-2,4-diamine		481.64 (M-H+)	2.17 (s, 3H), 2.33 (m, 4H), 2.48 (m, 4H), 2.65 (t, 2H), 3.98 (t, 2H), 6.03 (s, 2H), 6.10 (d, 1H), 6.68 (d, 2H), 6.93 (d, 1H), 7.04 (d, 1H), 7.48 (d, 2H), 7.96 (d, 1H), 8.86 (s, 1H), 8.90 (s, 1H)	
32	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-{4-[(3-fluorobenzyl) oxy]-3-methoxy phenyl} pyrimidine-2,4-diamine		495.44 (MH+)	3.62 (s, 3H), 5.01 (s, 2H), 5.97 (s, 2H), 6.08 (d, 1H), 6.75 (d, 1H), 6.90 (d, 1H), 7.03 (d, 1H), 7.16 (m, 2H), 7.27 (m, 2H), 7.43 (m, 1H), 7.96 (d, 1H), 8.86 (s, 1H), 8.89 (s, 1H)	
33	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-{4-[(2-fluorobenzyl) oxy]-3-methoxy phenyl} pyrimidine-2,4-diamine		495.43 (MH+)	3.62 (s, 3H), 5.01 (s, 2H), 5.97 (s, 2H), 6.08 (d, 1H), 6.75 (d, 1H), 6.90 (d, 1H), 7.03 (d, 1H), 7.16 (m, 2H), 7.27 (m, 2H), 7.43 (m, 1H), 7.96 (d, 1H), 8.86 (s, 1H), 8.89 (s, 1H)	

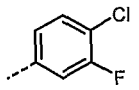
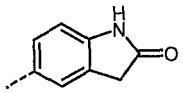
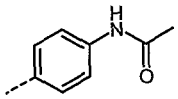
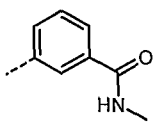
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
34	4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-(2-methoxyethyl) benzene sulfonamide		478.4 (MH+)		
35	N-[4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino) phenyl]-N-methyl acetamide		412.5 (MH+)		
36	N-[5-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-2-methylphenyl] acetamide		412.49 (MH+)	2.04 (s, 3H), 2.08 (s, 3H), 6.03 (s, 2H), 6.12 (dd, 1H), 6.90 (m, 2H), 7.05 (d, 1H), 7.46 (m, 2H), 7.98 (d, 1H), 8.90 (s, 1H), 8.97 (s, 1H), 9.17 (s, 1H)	
37	N-[4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino) benzyl] acetamide		412.5 (MH+)		

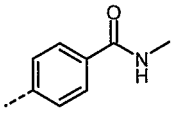
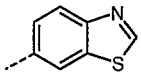
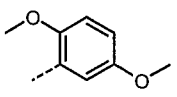
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
38	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~[3-(methylsulfonyl)phenyl] pyrimidine-2,4-diamine		419.45 (MH+)	3.12 (s, 3H), 6.05 (s, 2H), 6.21 (d, 1H), 6.94 (d, 1H), 7.06 (d, 1H), 7.37 (m, 2H), 8.10 (m, 3H), 9.06 (s, 1H), 9.47 (s, 1H)	
39	4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino] pyrimidin-2-yl}amino) benzene sulfonamide		420.46 (MH+)	6.05 (s, 2H), 6.22 (d, 1H), 6.96 (d, 1H), 7.10 (m, 3H), 7.54 (d, 2H), 7.86 (d, 2H), 8.07 (d, 1H), 9.13 (s, 1H), 9.54 (s, 1H)	
40	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino) benzene sulfonamide		420.45 (MH+)	6.06 (s, 2H), 6.17 (d, 1H), 6.93 (d, 1H), 7.07 (d, 1H), 7.27 (m, 4H), 7.98 (d, 1H), 8.04 (d, 1H), 8.09 (s, 1H), 9.02 (s, 1H), 9.42 (s, 1H)	
41	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~[4-(trifluoromethoxy)phenyl] pyrimidine-2,4-diamine		425.44 (MH+)	6.02 (s, 2H), 6.19 (d, 1H), 6.94 (d, 1H), 7.07 (m, 3H), 7.70 (d, 2H), 8.03 (d, 1H), 9.04 (s, 1H), 9.30 (s, 1H)	

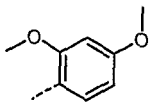
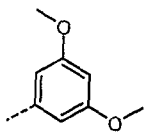
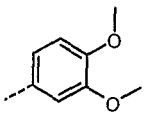
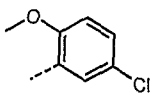
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
42	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(4-morpholin-4-ylphenyl) pyrimidine-2,4-diamine		426.47 (MH+)	3.00 (m, 4H), 3.75 (m, 4H), 6.00 (s, 2H), 6.07 (d, 1H), 6.73 (d, 2H), 6.92 (d, 1H), 7.03 (d, 1H), 7.46 (d, 2H), 7.94 (d, 1H), 8.80 (s, 1H), 8.88 (s, 1H)	
43	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(2-morpholin-4-ylphenyl) pyrimidine-2,4-diamine		426.47 (MH+)	2.80 (m, 4H), 3.78 (m, 4H), 6.03 (s, 2H), 6.18 (d, 1H), 6.90 (m, 2H), 6.96 (d, 1H), 7.07 (d, 1H), 7.20 (m, 1H), 8.03 (m, 2H), 8.18 (m, 1H), 9.13 (s, 1H)	
44	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(3-morpholin-4-ylphenyl) pyrimidine-2,4-diamine		426.46 (MH+)		
45	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~[4-(2-ethoxyethoxy) phenyl] pyrimidine-2,4-diamine		429.42 (MH+)	1.15 (t, 3H), 3.53 (q, 4H), 3.68 (m, 2H), 4.00 (m, 2H), 6.03 (s, 2H), 6.10 (d, 1H), 6.70 (d, 2H), 6.93 (d, 1H), 7.04 (d, 1H), 7.50 (d, 2H), 7.96 (d, 1H), 9.88 (s, 1H), 9.90 (s, 1H)	

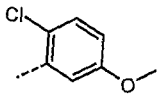
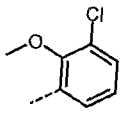
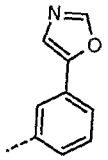
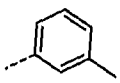
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
46	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(2,3,4-trimethoxy phenyl) pyrimidine-2,4-diamine		431.41 (MH+)	3.75 (s, 6H), 3.81 (s, 3H), 6.02 (s, 2H), 6.10 (d, 1H), 6.53 (d, 1H), 6.93 (d, 1H), 7.05 (d, 1H), 7.50 (s, 1H), 7.64 (d, 1H), 7.96 (d, 1H), 8.98 (s, 1H)	
47	N-[3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino) phenyl]methane sulfonamide		434.37 (MH+)	2.98 (s, 3H), 6.04 (s, 2H), 6.13 (d, 1H), 6.71 (d, 1H), 6.92 (d, 1H), 7.05 (m, 2H), 7.42 (s, 1H), 7.57 (d, 1H), 8.00 (d, 1H), 8.90 (s, 1H), 9.11 (s, 1H)	
48	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-[3-(dimethylamino)phenyl] pyrimidine-2,4-diamine		384.51 (MH+)		
49	2-[4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino) phenyl]ethanol		385.49 (MH+)	2.52 (t, 2H), 3.55 (q, 2H), 4.55 (t, 1H), 6.02 (s, 2H), 6.13 (d, 1H), 6.95 (m, 3H), 7.05 (d, 1H), 7.51 (d, 2H), 7.98 (d, 1H), 8.93 (s, 1H), 9.97 (s, 1H)	

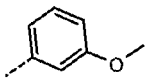
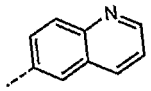
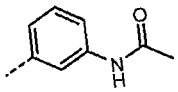
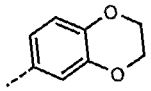
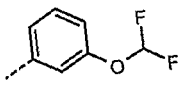
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
50	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(3-chloro-4-fluorophenyl) pyrimidine-2,4-diamine		393.43 (M+)	6.05 (s, 2H), 6.22 (d, 1H), 6.94 (d, 1H), 7.07 (d, 1H), 7.16 (t, 1H), 7.49 (m, 1H), 7.96 (m, 1H), 8.04 (d, 1H), 9.08 (s, 1H), 9.32 (s, 1H)	
51	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(4-chloro-2-fluorophenyl) pyrimidine-2,4-diamine		393.46 (M+)	6.03 (s, 2H), 6.18 (d, 1H), 6.93 (d, 1H), 7.00 (d, 1H), 7.05 (d, 1H), 7.34 (dd, 1H), 7.89 (t, 1H), 8.00 (d, 1H), 8.51 (s, 1H), 9.03 (s, 1H)	
52	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(3-chloro-2-fluorophenyl) pyrimidine-2,4-diamine		393.46 (M+)	6.02 (s, 2H), 6.19 (d, 1H), 6.90 (d, 1H), 6.96 (m, 1H), 7.03 (d, 1H), 7.15 (m, 1H), 7.81 (m, 1H), 8.00 (d, 1H), 8.65 (s, 1H), 9.04 (s, 1H)	
53	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(5-chloro-2-fluorophenyl) pyrimidine-2,4-diamine		393.46 (M+)	6.03 (s, 2H), 6.24 (d, 1H), 6.90 (d, 1H), 6.98 (m, 1H), 7.05 (d, 1H), 7.20 (dd, 1H), 8.04 (m, 2H), 8.47 (s, 1H), 9.11 (s, 1H)	

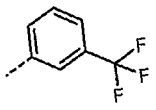
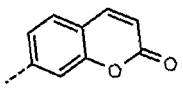
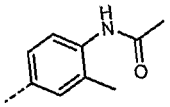
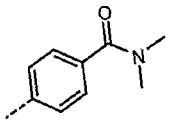
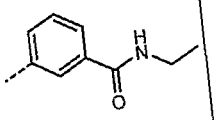
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
54	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(4-chloro-3-fluorophenyl) pyrimidine-2,4-diamine		393.46 (M+)	6.05 (s, 2H), 6.23 (d, 1H), 6.95 (d, 1H), 7.07 (d, 1H), 7.30 (m, 2H), 7.88 (d, 1H), 8.05 (d, 1H), 9.14 (s, 1H), 9.51 (s, 1H)	
55	5-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino) -1,3-dihydro-2H-indol-2-one		396.51 (MH+)	6.02 (s, 2H), 6.12 (d, 1H), 6.59 (d, 1H), 6.95 (d, 1H), 7.06 (d, 1H), 7.28 (d, 1H), 7.57 (s, 1H), 7.97 (d, 1H), 8.93 (s, 1H), 8.95 (s, 1H), 10.12 (s, 1H)	
56	N-[4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino) phenyl] acetamide		398.53 (MH+)	6.03 (s, 2H), 6.12 (d, 1H), 6.92 (d, 1H), 7.06 (d, 1H), 7.20 (d, 2H), 7.62 (d, 2H), 7.98 (d, 1H), 8.94 (s, 1H), 9.00 (s, 1H), 9.70 (s, 1H)	
57	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino) -N-methyl benzamide		398.53 (MH+)		

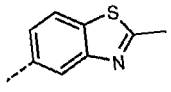
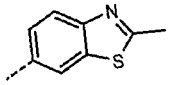
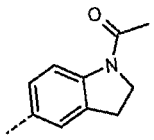
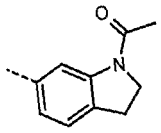
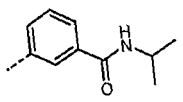
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
58	4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino) -N-methyl benzamide		398.49 (MH+)	2.78 (d, 3H), 6.04 (s, 2H), 6.22 (d, 1H), 6.97 (d, 1H), 7.08 (d, 1H), 7.60 (d, 2H), 7.68 (d, 2H), 8.05 (d, 1H), 8.16 (m, 1H), 9.07 (s, 1H), 9.38 (s, 1H)	
59	N~2~-1,3-benzothiazol-6-yl-N~4~-(5-chloro-1,3-benzodioxol-4-yl)pyrimidine-2,4-diamine		398.44 (MH+)	6.10 (s, 2H), 6.30 (d, 1H), 7.09 (d, 1H), 7.19 (d, 1H), 7.63 (dd, 1H), 7.92 (d, 1H), 8.15 (d, 1H), 8.63 (s, 1H), 9.19 (m, 2H), 9.56 (s, 1H)	
60	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(2,5-dimethoxy phenyl) pyrimidine-2,4-diamine		401.48 (MH+)	3.59 (s, 3H), 3.81 (s, 3H), 6.02 (s, 2H), 6.17 (d, 1H), 6.44 (dd, 1H), 6.90 (m, 2H), 7.04 (d, 1H), 7.43 (s, 1H), 7.88 (m, 1H), 8.02 (d, 1H), 9.07 (s, 1H)	

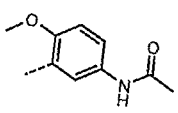
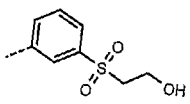
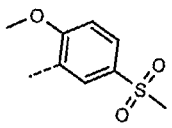
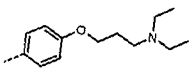
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
61	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(2,4-dimethoxy phenyl) pyrimidine-2,4-diamine		401.47 (MH+)	3.74 (s, 3H), 3.82 (s, 3H), 6.01 (s, 2H), 6.09 (d, 1H), 6.30 (dd, 1H), 6.59 (m, 1H), 6.93 (d, 1H), 7.06 (d, 1H), 7.31 (s, 1H), 7.85 (d, 1H), 7.96 (d, 1H), 8.96 (s, 1H)	
62	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(3,5-dimethoxy phenyl) pyrimidine-2,4-diamine		401.48 (MH+)	3.63 (s, 6H), 6.02 (s, 2H), 6.13 (d, 1H), 6.88 (d, 1H), 7.95 (m, 2H), 7.03 (d, 1H), 8.01 (d, 1H), 8.94 (s, 3H), 8.98 (s, 1H)	
63	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(3,4-dimethoxy phenyl) pyrimidine-2,4-diamine		401.48 (MH+)	3.59 (s, 3H), 3.69 (s, 3H), 6.00 (s, 2H), 6.09 (d, 1H), 6.70 (d, 1H), 6.90 (d, 1H), 7.04 (d, 1H), 7.18 (dd, 1H), 7.30 (m, 1H), 7.96 (d, 1H), 8.81 (s, 1H), 8.89 (s, 1H)	
64	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(5-chloro-2-methoxyphenyl) pyrimidine-2,4-diamine		405.43 (M+)	3.87 (s, 3H), 6.03 (s, 2H), 6.24 (d, 1H), 6.80 (m, 2H), 6.98 (d, 1H), 7.06 (d, 1H), 7.53 (s, 1H), 8.04(d, 1H), 8.20 (m, 1H), 9.18 (s, 1H)	

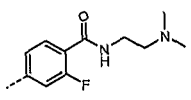
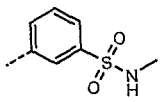
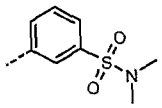
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
65	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(2-chloro-5-methoxyphenyl) pyrimidine-2,4-diamine		405.43 (M+)	3.63 (s, 3H), 6.00 (s, 2H), 6.19 (d, 1H), 6.60 (dd, 1H), 6.90 (d, 1H), 7.02 (d, 1H), 7.32 (d, 1H), 7.70 (s, 1H), 7.79 (m, 1H), 8.03 (d, 1H), 9.10 (s, 1H)	
66	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(3-chloro-2-methoxyphenyl) pyrimidine-2,4-diamine		405.43 (M+)	3.88 (s, 3H), 6.11 (s, 2H), 6.28 (d, 1H), 6.94 (m, 1H), 7.03 (d, 1H), 7.08 (d, 1H), 7.16 (d, 1H), 7.86 (s, 1H), 8.11 (d, 1H), 8.16 (d, 1H), 9.24 (s, 1H)	
67	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-[3-(1,3-oxazol-5-yl)phenyl] pyrimidine-2,4-diamine		408.46 (M+)	5.98 (s, 2H), 6.18 (d, 1H), 6.85 (d, 1H), 7.03 (d, 1H), 7.20 (m, 2H), 7.47 (s, 1H), 7.70 (m, 1H), 7.94 (s, 1H), 8.03 (d, 1H), 8.40 (s, 1H), 9.00 (s, 1H), 9.23 (s, 1H)	
80	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(3-methylphenyl) pyrimidine-2,4-diamine		355.19 (M+)		

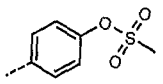
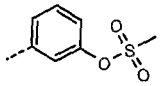
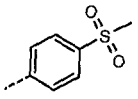
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
81	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(3-methoxyphenyl) pyrimidine-2,4-diamine		371.42 (M+)		
82	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~-quinolin-6-yl pyrimidine-2,4-diamine		392.09 (M+)		
83	N-[3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino) phenyl] acetamide		398.09 (M+)		
84	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(2,3-dihydro-1,4-benzodioxin-6-yl)pyrimidine-2,4-diamine		399.10 (M+)		
85	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~[3-(difluoro methoxy)phenyl]pyrimidine-2,4-diamine		407.05 (M+)		

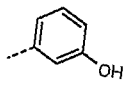
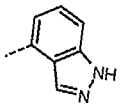
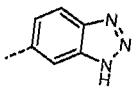
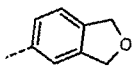
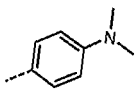
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
86	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~[3-(trifluoromethyl)phenyl] pyrimidine-2,4-diamine		408.90 (M+)		
87	6-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-2H-chromen-2-one		408.94 (M+)		
88	N-[4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino) -2-methyl phenyl] acetamide		411.95 (M+)		
89	4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N,N-dimethyl benzamide		411.96 (M+)		
90	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino) – N-ethyl benzamide		411.98 (M+)		

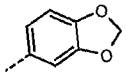
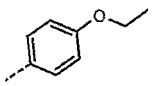
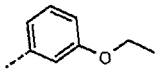
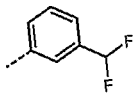
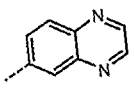
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
91	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(2-methyl-1,3-benzothiazol-5-yl)pyrimidine-2,4-diamine		411.93 (M+)		
92	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(2-methyl-1,3-benzothiazol-6-yl)pyrimidine-2,4-diamine		411.93 (M+)		
93	N~2~~(1-acetyl-2,3-dihydro-1H-indol-5-yl)-N~4~~(5-chloro-1,3-benzodioxol-4-yl)pyrimidine-2,4-diamine		423.97 (M+)		
94	N~2~~(1-acetyl-2,3-dihydro-1H-indol-6-yl)-N~4~~(5-chloro-1,3-benzodioxol-4-yl)pyrimidine-2,4-diamine		423.95 (M+)		
95	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-isopropyl benzamide		425.95 (M+)		

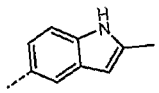
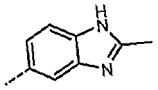
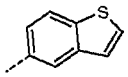
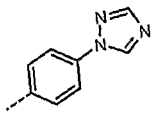
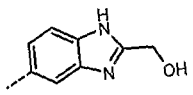
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
96	N-[3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino) -4-methoxy phenyl] acetamide		427.93 (M+)		
97	2-{[3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino) phenyl]sulfonyl}ethanol		449.39 (M+)		
98	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-[2-methoxy-5-(methylsulfonyl)phenyl] pyrimidine-2,4-diamine		449.38 (M+)		
99	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-{4-[3-(diethylamino) propoxy]phenyl}pyrimidine-2,4-diamine		470.50 (M+)		

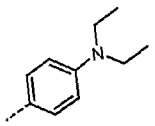
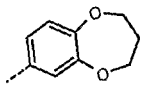
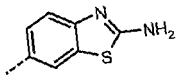
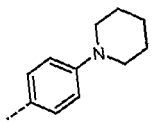
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
100	4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-[2-(dimethylamino)ethyl]-2-fluoro benzamide		473.47 (M+)		
101	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-methylbenzene sulfonamide		434.38 (M+)	(300 MHz) 2.70 (s, 3H), 6.04 (s, 2H), 6.18 (d, 1H), 6.92 (d, 1H), 7.05 (d, 1H), 7.25 (d, 1H), 7.29 (d, 1H), 7.31 - 8.00 (m, 1H), 8.03 - 8.05 m, (3H), 9.02 (s, 1H), 9.42 (s, 1H)	
102	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N,N-dimethyl benzene sulfonamide		448.39 (M+)	(300 MHz) 2.60 (s, 6H), 6.04 (s, 2H), 6.21 (d, 1H), 6.92 (d, 1H), 7.05 (d, 1H), 7.18 (d, 1H), 7.32 (t, 1H), 7.94 (s, 1H), 8.04 (d, 1H), 8.15 (d, 1H), 9.04 (s, 1H), 9.42 (s, 1H)	

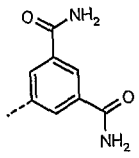
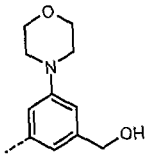
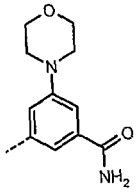
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
103	4-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino) phenylmethane sulfonate		435.36 (M+)	(300 MHz) 3.30 (3H, under water), 6.02 (s, 2H), 6.17 (d, 1H), 6.93 (d, 1H), 7.04 (s, 1H, 7.04 - 7.08 (m, 2H), 7.68 (d, 2H), 8.01 (d, 1H), 9.03 (s, 1H), 9.28 (s, 1H)	
104	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino) phenylmethane sulfonate		435.46 (M+)	(300 MHz) 3.37 (3H, under water), 6.02 (s, 2H), 6.18 (d, 1H), 6.80 - 6.83 (m, 1H), 6.91 (d, 1H), 7.05 (d, 1H), 7.18 (t, 1H), 7.61 - 7.65 (d, 2H), 8.03 (d, 1H), 9.04 (s, 1H), 9.33 (s, 1H)	
105	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-[4-(methylsulfonyl)phenyl] pyrimidine-2,4-diamine		419.37 (M+)	(300 MHz) 3.10 (s, 3H), 6.04 (s, 2H), 6.26 (d, 1H), 6.97 (d, 1H), 7.08 (d, 1H), 7.60 (d, 2H), 7.84 (d, 2H), 8.07 (d, 1H), 9.16 (s, 1H), 9.69 (s, 1H)	

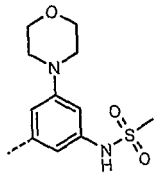
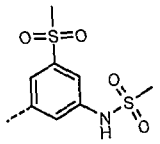
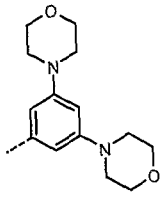
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
106	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino) phenol		357.40 (M+)		
107	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-1H-indazol-4-yl pyrimidine-2,4-diamine		381.08 (M+)		
108	N~2~-1H-1,2,3-benzotriazol-5-yl-N~4~-(5-chloro-1,3-benzodioxol-4-yl)pyrimidine-2,4-diamine		382.08 (M+)		
109	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(1,3-dihydro-2-benzofuran-5-yl)pyrimidine-2,4-diamine		383.10 (M+)		
110	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-[4-(dimethylamino) phenyl] pyrimidine-2,4-diamine		384.12 (M+)		

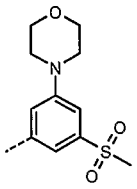
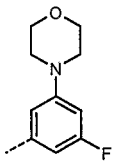
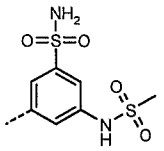
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
111	N~2~~1,3-benzodioxol-5-yl-N~4~~(5-chloro-1,3-benzodioxol-4-yl)pyrimidine-2,4-diamine		385.08 (M+)		
112	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(4-ethoxyphenyl) pyrimidine-2,4-diamine		385.12 (M+)		
113	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(3-ethoxyphenyl) pyrimidine-2,4-diamine		385.12 (M+)		
114	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~[3-(difluoromethyl) phenyl] pyrimidine-2,4-diamine		391.09 (M+)		
115	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~quinoxalin-6-ylpyrimidine-2,4-diamine		393.09 (M+)		

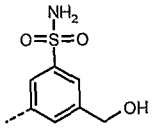
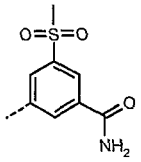
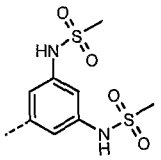
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
116	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(2-methyl-1H-indol-5-yl) pyrimidine-2,4-diamine		394.13 (M+)		
117	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(2-methyl-1H-benzimidazol-6-yl)pyrimidine-2,4-diamine		393.10 (M+)		
118	N~2~~1-benzothien-5-yl-N~4~~(5-chloro-1,3-benzodioxol-4-yl)pyrimidine-2,4-diamine		397.08 (M+)		
119	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~[4-(1H-1,2,4-triazol-1-yl)phenyl] pyrimidine-2,4-diamine		408.10 (M+)		
120	[5-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-1H-benzimidazol-2-yl]methanol		411.12 (M+)		

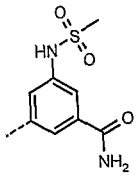
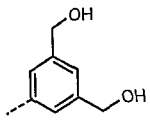
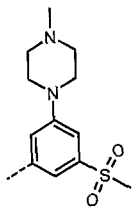
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
121	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~[4-(diethylamino) phenyl] pyrimidine-2,4-diamine		412.18 (M+)		
122	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)pyrimidine-2,4-diamine		413.13 (M+)		
123	N~6~~{4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}-1,3-benzothiazole-2,6-diamine		411.05 (M-H+)		
124	N~4~~(5-chloro-1,3-benzodioxol-4-yl)-N~2~~(4-piperidin-1-ylphenyl) pyrimidine-2,4-diamine		424.18 (M+)		

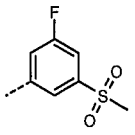
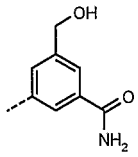
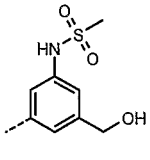
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
125	5-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino] benzene-1,3-dicarboxamide		427.41 (M+)	6.04 (s, 2H), 6.10 (d, 1H), 6.85 (d, 1H), 7.00 (d, 1H), 7.30 (br s, 2H), 7.73 (br s, 2H), 7.78 (s, 1H), 8.02 (d, 1H), 8.20 (s, 2H), 8.93 (s, 1H), 9.18 (s, 1H)	
126	[3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino]-5-morpholin-4-yl-phenyl] methanol		456.38 (M+)	2.96 (m, 4H), 3.70 (m, 4H), 4.28 (d, 2H), 4.93 (t, 1H), 5.97 (s, 2H), 6.10 (d, 1H), 6.48 (s, 1H), 6.89 (d, 1H), 7.05 (m, 3H), 7.97 (d, 1H), 8.80 (s, 1H), 8.88 (s, 1H)	10
127	3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino]-5-morpholin-4-yl-benzamide		469.40 (M+)	3.00 (m, 4H), 3.72 (m, 4H), 5.97 (s, 2H), 6.09 (d, 1H), 6.85 (d, 1H), 6.93 (s, 1H), 7.00 (d, 1H), 7.14 (s, 1H), 7.46 (s, 1H), 7.53 (s, 1H), 7.67 (s, 1H), 8.00 (d, 1H), 8.87 (s, 1H), 8.91 (s, 1H)	8h

No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
128	N-[3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino]-5-morpholin-4-yl-phenyl] methane sulfonamide		518.35 (M+)	2.93 (m, 4H), 3.00 (s, 3H), 3.70 (m, 4H), 6.00 (s, 2H), 6.10 (d, 1H), 6.31 (m, 1H), 6.87 (d, 1H), 7.04 (m, 2H), 7.15 (s, 1H), 7.98 (d, 1H), 8.80 (s, 1H), 8.88 (s, 1H), 9.32 (br s, 1H)	14
129	N-[3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino]-5-methylsulfonyl-phenyl] methane sulfonamide		512.31 (M+)	3.07 (s, 3H), 3.11 (s, 3H), 6.06 (s, 2H), 6.18 (d, 1H), 6.88 (d, 1H), 7.02 (d, 1H), 7.20 (m, 1H), 7.90 (m, 1H), 8.05 (m, 2H), 8.83 (s, 1H), 9.45 (s, 1H), 10.00 (br s, 1H)	9
130	N'-(5-chlorobenzo[1,3]dioxol-4-yl)-N-(3,5-dimorpholin-4-ylphenyl)pyrimidine-2,4-diamine		511.50 (M+)	2.95 (m, 8H), 3.70 (m, 8H), 5.96 (s, 2H), 6.07 (m, 2H), 6.81 (d, 2H), 6.86 (d, 1H), 7.02 (d, 1H), 7.97 (d, 1H), 8.65 (s, 1H), 8.84 (s, 1H)	8f

No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
131	N'-(5-chlorobenzo[1,3]dioxol-4-yl)-N-(3-methylsulfonyl-5-morpholin-4-yl-phenyl) pyrimidine-2,4-diamine		504.4 (M+)	3.07 (m, 4H), 3.09 (s, 3H), 3.72 (m, 4H), 6.00 (s, 2H), 6.15 (d, 1H), 6.90 (m, 2H), 7.02 (d, 1H), 7.64 (s, 1H), 7.72 (s, 1H), 8.04 (d, 1H), 8.97 (s, 1H), 9.21 (s, 1H)	8b
132	N'-(5-chlorobenzo[1,3]dioxol-4-yl)-N-(3-fluoro-5-morpholin-4-yl-phenyl) pyrimidine-2,4-diamine		444.44 (M+)	3.00 (m, 4H), 3.70 (m, 4H), 5.99 (s, 2H), 6.15 (d, 1H), 6.24 (m, 1H), 6.86 (m, 2H), 7.02 (d, 1H), 7.19 (d, 1H), 8.00 (d, 1H), 8.99 (s, 1H), 9.05 (s, 1H)	8a
133	3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino]-5-methanesulfonamido-benzenesulfonamide		513.35 (M+)	5.10 (s+m, 3H), 6.88 (d, 1H), 7.03 (d, 1H), 7.20 (m, 1H), 7.30 (s, 2H), 7.80 (m, 1H), 8.02 (d, 1H), 8.09 (m, 1H), 8.86 (s, 1H), 9.40 (s, 1H), 9.88 (br s, 1H)	9a

No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
134	3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino]-5-(hydroxymethyl)benzene sulfonamide		450.37 (M+)	4.40 (d, 2H), 5.26 (t, 1H), 6.03 (s, 2H), 6.13 (d, 1H), 6.90 (d, 1H), 7.03 (d, 1H), 7.22 (s, 2H), 7.36 (s, 1H), 7.85 (s, 1H), 8.00 (m, 2H), 8.96 (s, 1H), 9.37 (s, 1H)	16
135	3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino]-5-methylsulfonyl-benzamide		462.36 (M+)	3.16 (s, 3H), 6.04 (s, 2H), 6.18 (d, 1H), 6.87 (d, 1H), 7.01 (d, 1H), 7.46 (s, 1H), 7.83 (s, 1H), 8.00 (s, 1H), 8.06 (d, 1H), 8.40 (s, 1H), 8.46 (s, 1H), 9.01 (s, 1H), 9.51 (s, 1H)	8m
136	N-[3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino]-5-methanesulfonamido-phenyl] methanesulfonamide		527.34 (M+)	3.00 (s, 6H), 6.06 (s+m, 3H), 6.67 (m, 1H), 6.86 (d, 1H), 7.02 (d, 1H), 7.39 (m, 2H), 7.98 (d, 1H), 8.75 (s, 1H), 9.08 (s, 1H), 9.55 (br s, 2H)	8i

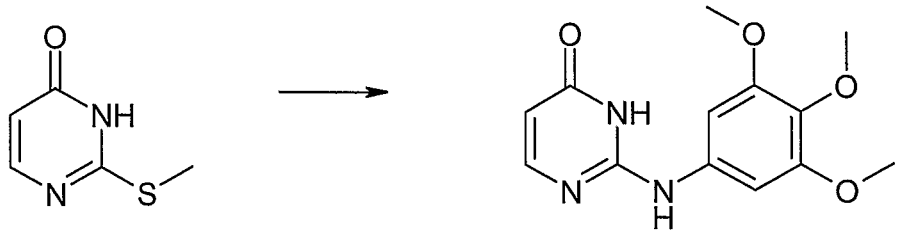
No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
137	3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino]-5-methanesulfonamido-benzamide		477.38 (M+)	3.02 (s, 3H), 6.05 (s, 2H), 6.09 (d, 1H), 6.85 (d, 1H), 7.01 (d, 1H), 7.14 (m, 1H), 7.23 (br s, 1H), 7.65 (br s, 1H), 7.70 (m, 1H), 7.84 (s, 1H), 8.00 (d, 1H), 8.84 (s, 1H), 9.12 (s, 1H), 9.59 (br s, 1H)	8j
138	[3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino]-5-(hydroxymethyl)phenyl] methanol		401.43 (M+)	4.30 (d, 4H), 4.96 (t, 2H), 5.97 (s, 2H), 6.10 (d, 1H), 6.87 (m, 2H), 7.04 (d, 1H), 7.39 (s, 2H), 7.98 (d, 1H), 8.90 (s, 1H), 8.98 (s, 1H)	8l
139	N'-(5-chlorobenzo[1,3]dioxol-4-yl)-N-[3-(4-methylpiperazin-1-yl)-5-methylsulfonyl-phenyl]pyrimidine-2,4-diamine		517.48 (M+)		8d

No.	Name	R^4	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)	Aniline (Method)
140	N'-(5-chlorobenzo[1,3]dioxol-4-yl)-N-(3-fluoro-5-methylsulfonyl-phenyl)pyrimidine-2,4-diamine		437.42 (M+)	3.18 (s, 3H), 6.02 (s, 2H), 6.25 (d, 1H), 6.92 (d, 1H), 7.04 (d, 1H), 7.16 (m, 1H), 7.82 (s, 1H), 8.06 (d, 1H), 8.12 (m, 1H), 9.16 (s, 1H), 9.74 (s, 1H)	8
141	3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino]-5-(hydroxymethyl) benzamide		414.36 (M+)		8k
142	N-[3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino]-5-(hydroxymethyl)phenyl] methane sulfonamide		462.31 (M+)	2.96 (s, 3H), 4.29 (m, 2H), 5.04 (t, 1H), 6.02 (s, 2H), 6.10 (d, 1H), 6.75 (m, 1H), 6.87 (d, 1H), 7.03 (d, 1H), 7.31 (m, 1H), 7.43 (s, 1H), 7.98 (d, 1H), 8.84 (s, 1H), 9.03 (s, 1H), 9.45 (br s, 1H)	15a

Example 3

Step 1

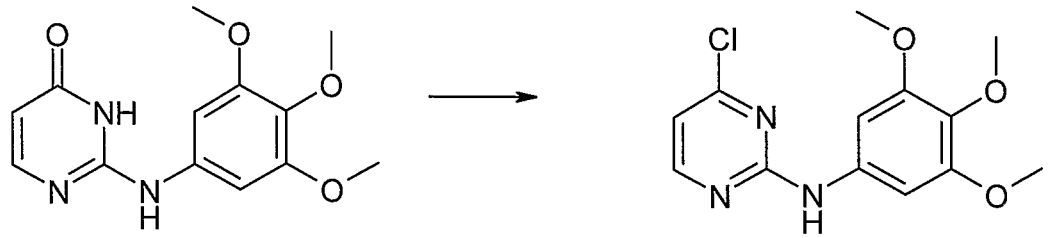
2-[(3,4,5-Trimethoxyphenyl)amino]pyrimidin-4(3*H*)-one



3, 4, 5-Trimethoxyaniline (6.82 g) and 2-(methylthio)pyrimidin-4(3*H*)-one (5.26 g) were suspended in diglyme (50 ml) and heated at 165°C for 18 hours under nitrogen to give a red solution. The reaction was cooled to room temperature then poured into 500 ml diethyl ether with stirring to give an oily precipitate that was filtered and re-dissolved in water (250 ml). A solid precipitate formed which was stirred for 30 minutes then filtered to give the title compound as a cream solid (3.80 g, 37%); NMR Spectrum (300 MHz, DMSO) 3.63 (s, 3H), 3.76 (s, 6H), 5.80 (d, 1H), 6.95 (s, 2H), 7.76 (d, 1H); Mass Spectrum MH^+ 278.5.

Step 2

4-Chloro-*N*-(3,4,5-trimethoxyphenyl)pyrimidin-2-amine

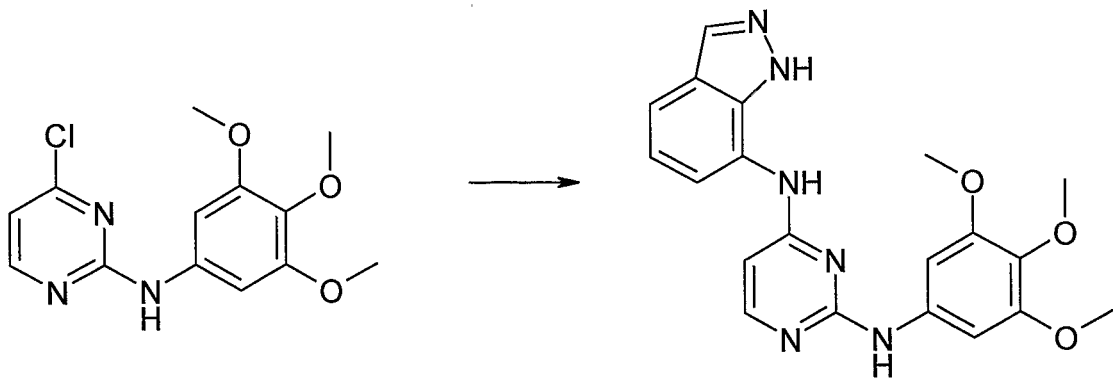


2-[(3,4,5-Trimethoxyphenyl)amino]pyrimidin-4(3*H*)-one (4.7 g) was suspended in acetonitrile (100 ml). Phosphorous oxychloride (10 ml) was added dropwise to give a dark solution. The reaction was heated at 85°C for 2.5 hours then further phosphorous oxychloride (2 ml) added and the reaction heated overnight. The reaction was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in DCM (150 ml) and to ice water (100 ml) added. The mixture was stirred while adding saturated sodium

bicarbonate solution to give *p*H = 8. The organic layer was separated, washed with brine (25 ml), dried and concentrated to give a yellow solid. This was triturated with iso-hexane and filtered to give the title compound as a yellow solid (4.07 g, 81%); NMR Spectrum (300 MHz, DMSO) 3.63 (s, 3H), 3.76 (s, 6H), 6.94 (d, 1H), 7.13 (s, 2H), 8.43 (d, 1H), 9.87 (s, 1H); Mass Spectrum MH^+ 296.5.

Step 3

***N*~4~-(1*H*-Indazol-7-yl)-*N*~2~-(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine (Compound No. 68)**



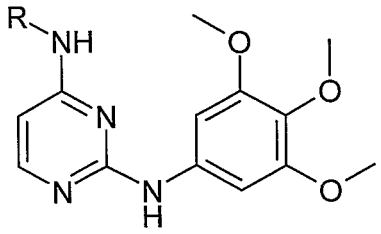
Compound 68

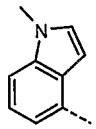
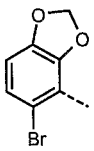
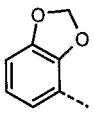
7-Aminoindazole (33 mg) and 4-chloro-*N*-(3,4,5-trimethoxyphenyl)pyrimidin-2-amine (70 mg) were dissolved in NMP (1 ml) and a solution of HCl in dioxane (0.07 ml, 4M) added. The reaction was heated at 130°C for 5 hours then cooled to room temperature and concentrated in vacuo. The residue was purified by reverse phase chromatography to give the title compound as a solid (44 mg, 47%); NMR Spectrum (300 MHz, DMSO) 3.58 (s, 6H), 3.61 (s, 3H), 6.18 (d, 1H), 7.09 (m, 3H), 7.54 (d, 1H), 7.71 (d, 1H), 8.05 (d, 1H), 8.10 (s, 1H), 8.95 (s, 1H), 9.11 (s, 1H), 12.82 (s, 1H); Mass Spectrum M^+ 392.4.

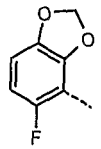
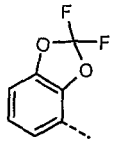
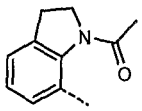
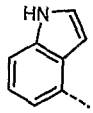
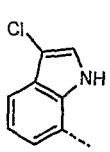
Example 4

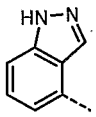
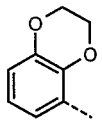
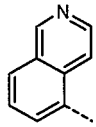
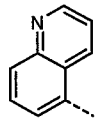
The procedure described in example 3 above was repeated using the appropriate aniline. Thus were obtained the compounds described below in **Table 2**.

Table 2



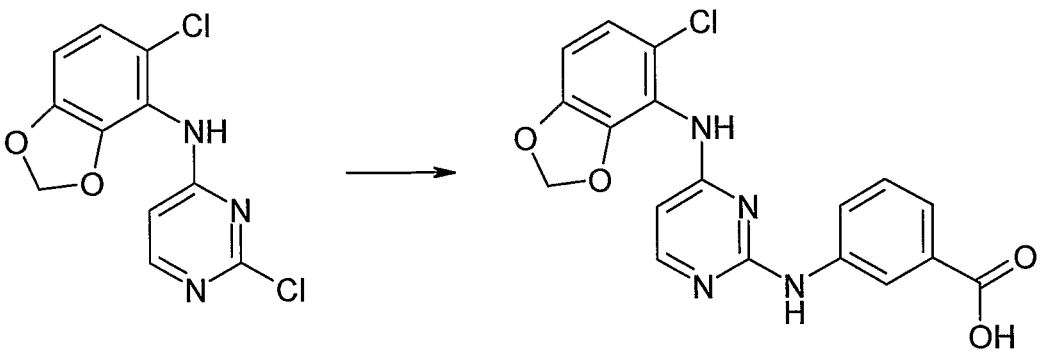
No.	Name	R	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)
69	N'-(1-methylindol-4-yl)-N-(3,4,5-trimethoxyphenyl)-pyrimidine-2,4-diamine		406.6 (MH+)	
70	N'-(5-bromobenzo[1,3]dioxol-4-yl)-N-(3,4,5-trimethoxyphenyl)-pyrimidine-2,4-diamine		477.4 (M+)	3.58 (s, 9H), 6.20 (d, 1H), 7.02 (s, 2H), 7.67 (d, 1H), 8.00 (d, 1H), 8.05 (d, 1H), 8.71 (s, 1H), 8.83 (s, 1H), 8.98 (s, 1H), 9.56 (s, 1H)
71	N'-benzo[1,3]dioxol-4-yl-N-(3,4,5-trimethoxyphenyl)-pyrimidine-2,4-diamine		397.5 (MH+)	3.53 (s, 3H), 3.59 (s, 6H), 6.15 (d, 1H), 7.03 (s, 2H), 7.40 (s, 1H), 7.60 (s, 1H), 8.01 (d, 1H), 8.97 (s, 1H), 9.29 (s, 1H)

No.	Name	R	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)
72	N'-(5-fluorobenzo[1,3]dioxol-4-yl)-N-(3,4,5-trimethoxyphenyl)-pyrimidine-2,4-diamine		415.5 (MH+)	
73	N'-(2,2-difluorobenzo[1,3]dioxol-4-yl)-N-(3,4,5-trimethoxyphenyl)-pyrimidine-2,4-diamine		433.5 (MH+)	3.60 (s, 9H), 6.34 (d, 1H), 7.06 (s, 2H), 7.14 (d, 1H), 7.78 (d, 1H), 8.08 (d, 1H), 9.01 (s, 1H), 9.43 (s, 1H)
74	1-[7-[2-(3,4,5-trimethoxyphenyl)aminopyrimidin-4-yl]amino-2,3-dihydroindol-1-yl]ethanone		436.5 (MH+)	3.10 (t, 2H), 3.61 (s, 3H), 3.72 (s, 6H), 4.15 (t, 2H), 6.17 (d, 1H), 7.06 (d, 1H), 7.17 (m, 3H), 7.55 (d, 1H), 8.03 (d, 1H), 9.03 (s, 1H), 9.40 (s, 1H)
75	N'-(1H-indol-4-yl)-N-(3,4,5-trimethoxyphenyl)-pyrimidine-2,4-diamine		392.5 (MH+)	3.63 (s, 9H), 6.31 (d, 1H), 6.61 (m, 1H), 7.03 (t, 1H), 7.15 (m, 3H), 7.29 (m, 1H), 7.64 (d, 1H), 8.00 (d, 1H), 8.88 (s, 1H), 8.96 (s, 1H), 11.10 (s, 1H)
150	N'-(3-chloro-1H-indol-7-yl)-N-(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine		426.2 (MH+)	3.48 (s, 9H), 6.13 (d, 1H), 7.08 (m, 3H), 7.30 (d, 1H), 7.46 (s, 1H), 7.52 (d, 1H), 7.95 (s, 1H), 8.01 (d, 1H), 8.90 (s, 1H), 9.00 (s, 1H)

No.	Name	R	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)
151	N'-(1H-indazol-4-yl)-N-(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine		393.51 (MH+)	
152	N'-(7,10-dioxabicyclo[4.4.0]deca-2,4,11-trien-2-yl)-N-(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine		411.5 (MH+)	3.60 (s, 3H), 3.65 (s, 6H), 4.28 (m, 4H), 6.31 (d, 1H), 7.62 (dd, 1H), 6.75 (t, 1H), 7.12 (s, 2H), 7.55 (d, 1H), 7.98 (d, 1H), 8.52 (s, 1H), 8.88 (s, 1H)
153	N'-isoquinolin-5-yl-N-(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine		404.13 (MH+)	
154	N'-quinolin-5-yl-N-(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine		404.51 (MH+)	3.50 (s, 6H), 3.58 (s, 3H), 6.26 (d, 1H), 7.02 (s, 2H), 7.55 (dd, 1H), 7.75 (m, 1H), 7.90 (m, 2H), 8.04 (d, 1H), 8.47 (d, 1H), 8.82 (m, 2H), 9.34 (s, 1H)

Example 5

3-({4-[(5-Chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzoic acid



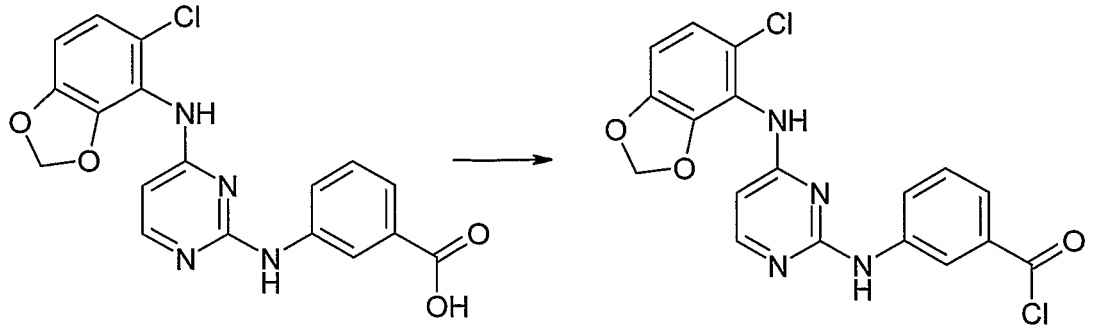
Compound 155

3-Aminobenzoic acid (6.1 g) and 2-chloro-*N*-(5-chloro-1,3-benzodioxol-4-yl)pyrimidin-4-amine (9 g) were dissolved in DMA (120 ml) and a solution of HCl in dioxane (11.1 ml, 4M) added. The reaction was heated at 96°C for 4 hours then cooled to room temperature and DIPEA (5 ml) added. The solution was concentrated in vacuo. Water was added and the resulting solid filtered and triturated with methanol and dried in vacuo to give the title compound as an off-white solid (9.8 g, 80%); NMR Spectrum (300 MHz, DMSO) 6.00 (s, 2H), 6.17 (d, 1H), 6.90 (d, 1H), 7.03 (d, 1H), 7.18 (t, 1H), 7.41 (d, 1H), 8.04 (m, 3H), 9.00 (s, 1H), 9.28 (s, 1H), 12.72 (br s, 1H); Mass Spectrum MH^+ 385.36.

Example 6

Step 1

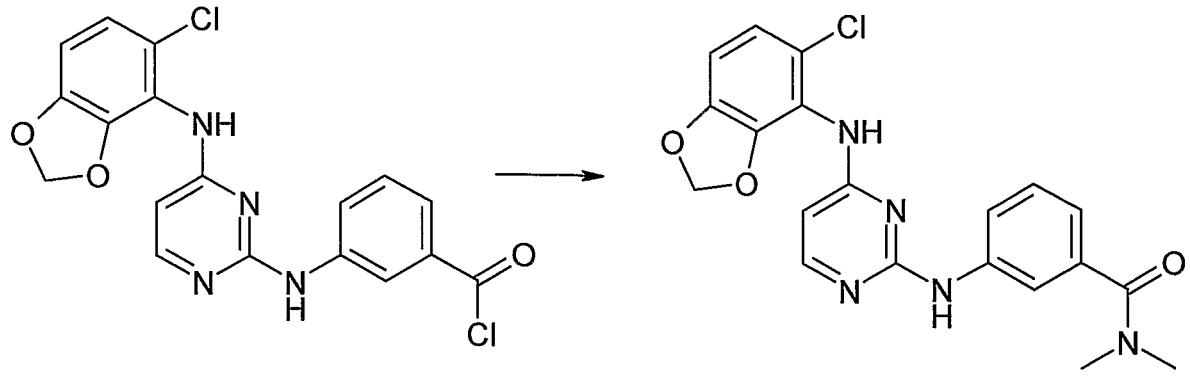
3-({4-[(5-Chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzoyl chloride



3-({4-[(5-Chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzoic acid (3.61 g, Example 5) was added to thionyl chloride (35 ml) at 0°C. One drop of DMF was added and the solution stirred at 0°C for 2 hours, then concentrated in vacuo and azeotroped with toluene to give the title compound as a yellow solid (3.7 g, 98%) which was used without further purification.

Step 2

3-({4-[(5-Chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-*N,N*-dimethylbenzamide



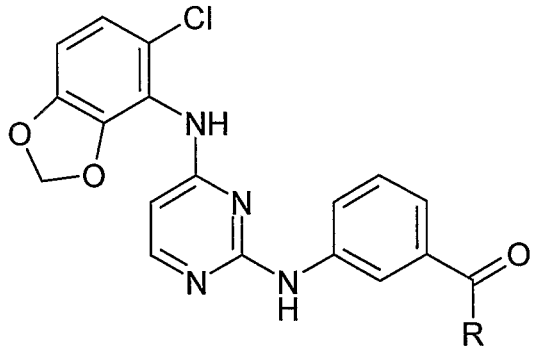
Compound 156

3-({4-[(5-Chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzoyl chloride (100 mg) was dissolved in dry THF (5 ml) and a dimethylamine (5 ml, 2M in THF) added and the reaction stirred at room temperature for 2 hours. The solution was concentrated in vacuo and the residue purified by reverse phase chromatography to give the title compound as a solid (61 mg, 52%); NMR Spectrum (300 MHz, DMSO) 2.84 (s, 3H), 2.97 (s, 3H), 6.00 (s, 2H), 6.16 (d, 1H), 6.79 (d, 1H), 6.90 (d, 1H), 7.02 (d, 1H), 7.13 (t, 1H), 7.58 (s, 1H), 7.69 (d, 1H), 8.00 (d, 1H), 8.98 (s, 1H), 9.20 (s, 1H); Mass Spectrum MH^+ 412.42.

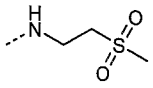
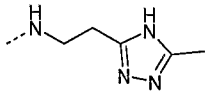
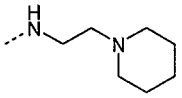
Example 7

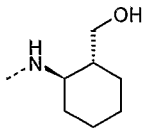
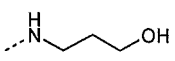
The procedure described in Example 6 above was repeated using the appropriate aniline. Thus were obtained the compounds described below in **Table 3**.

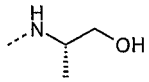
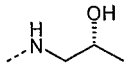
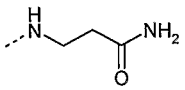
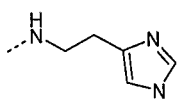
Table 3

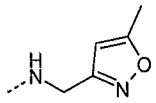
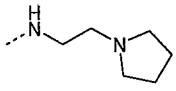
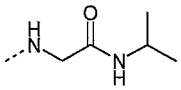


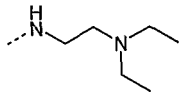
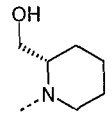
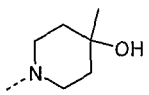
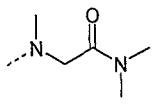
No	Name	R	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)
157	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-(3-hydroxy-2,2-dimethylpropyl) benzamide		470.44 (MH+)	0.84 (s, 6H), 3.14 (m, 2H), 3.32 (m, 2H), 4.62 (t, 1H), 6.01 (s, 2H), 6.15 (s, 1H), 6.90 (m, 1H), 7.03 (m, 1H), 7.15 (m, 1H), 7.26 (m, 1H), 7.87 (s, 1H), 7.94 (d, 1H), 8.00 (d, 1H), 8.18 (s, 1H), 8.98 (s, 1H), 9.14 (s, 1H)

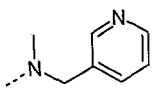
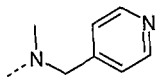
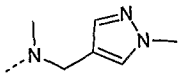
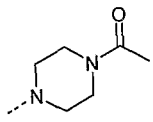
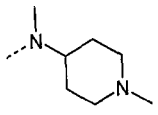
No	Name	R	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)
158	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-[2-(methylsulfonyl)ethyl] benzamide		490.44 (MH+)	3.04 (s, 3H), 3.30 (m, 2H), 3.65 (m, 2H), 6.01 (s, 2H), 6.15 (s, 1H), 6.90 (m, 1H), 7.03 (m, 1H), 7.15 (m, 1H), 7.26 (m, 1H), 7.90 (m, 2H), 8.00 (d, 1H), 8.50 (s, 1H), 8.98 (s, 1H), 9.14 (s, 1H)
160	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-[2-(3-methyl-1H-1,2,4-triazol-5-yl)ethyl]benzamide		493.48 (MH+)	
161	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-(2-piperidin-1-ylethyl)benzamide		494.99 (M+)	1.38 (m, 2H), 1.50 (m, 4H), 2.40 (m, 6H), 3.30 (m, 2H), 6.01 (s, 2H), 6.14 (s, 1H), 6.90 (m, 1H), 7.03 (m, 1H), 7.12 (m, 1H), 7.25 (m, 1H), 7.86 (s, 1H), 7.91 (d, 1H), 8.00 (m, 1H), 8.12 (s, 1H), 8.97 (s, 1H), 9.16 (s, 1H)

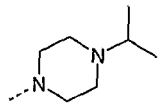
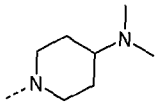
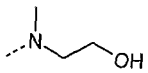
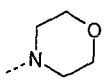
No	Name	R	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)
162	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-[(1R,2R)-2-(hydroxymethyl) cyclohexyl] benzamide		495.97 (M+)	1.09 (m, 2H), 1.20 (m, 1H), 1.40 (m, 1H), 1.63 (m, 2H), 1.78 (m, 1H), 2.35 (m, 2H), 3.52 (m, 1H), 4.21 (t, 1H), 5.97 (s, 2H), 6.08 (s, 1H), 6.82 (m, 1H), 6.95 (m, 1H), 7.05 (m, 1H), 7.19 (m, 1H), 7.75 (d, 1H), 7.88 (m, 1H), 7.93 (m, 1H), 7.99 (m, 1H), 8.88 (s, 1H), 9.06 (s, 1H)
163	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-[3-(dimethylamino)-2,2-dimethylpropyl] benzamide		497.00 (M+)	0.90 (s, 6H), 2.19 (m, 2H), 2.28 (s, 6H), 3.18 (s, 2H), 6.01 (s, 2H), 6.15 (s, 1H), 6.90 (m, 1H), 7.03 (m, 1H), 7.15 (m, 1H), 7.22 (m, 1H), 7.85 (m, 1H), 7.94 (d, 1H), 8.00 (s, 1H), 8.31 (s, 1H), 8.96 (s, 1H), 9.18 (s, 1H)
164	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-(3-hydroxypropyl) benzamide		442.51 (MH+)	1.69 (m, 2H), 3.30 (m, 2H), 3.48 (m, 2H), 6.01 (s, 2H), 6.15 (s, 1H), 6.90 (m, 1H), 7.03 (m, 1H), 7.12 (m, 1H), 7.25 (m, 1H), 7.85 (s, 1H), 7.92 (m, 1H), 8.01 (m, 1H), 8.20 (s, 1H), 8.96 (s, 1H), 9.15 (s, 1H)

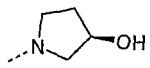
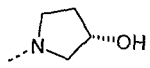
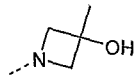
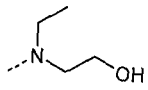
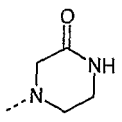
No	Name	R	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)
165	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-[(1S)-2-hydroxy-1-methylethyl] benzamide		442.51 (MH+)	
166	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-[(2R)-2-hydroxypropyl] benzamide		442.52 (MH+)	1.07 (d, 3H), 3.19 (m, 2H), 3.78 (m, 1H), 6.01 (s, 2H), 6.15 (s, 1H), 6.90 (m, 1H), 7.03 (m, 1H), 7.12 (m, 1H), 7.28 (m, 1H), 7.88 (s, 1H), 7.92 (m, 1H), 8.01 (m, 1H), 8.12 (s, 1H), 8.96 (s, 1H), 9.15 (s, 1H)
167	N-(2-carbamoylethyl)-3-[[4-[(5-chlorobenzo [1,3]dioxol-4-yl) amino]pyrimidin-2-yl]amino] benzamide		455.48 (MH+)	2.35 (m, 2H), 3.29 (m, 2H), 6.01 (s, 2H), 6.15 (s, 1H), 6.80 (s, 1H), 6.90 (m, 1H), 7.03 (m, 1H), 7.13 (m, 1H), 7.26 (m, 1H), 7.35 (s, 1H), 7.88 (s, 1H), 7.92 (m, 1H), 8.01 (m, 1H), 8.24 (s, 1H), 8.96 (s, 1H), 9.17 (s, 1H)
168	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-[2-(1H-imidazol-4-yl)ethyl]benzamide		476.21 (M-H+)	

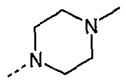
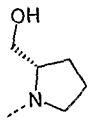
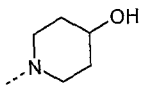
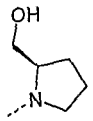
No	Name	R	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)
169	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-[(5-methylisoxazol-3-yl)methyl]benzamide		479.23 (MH+)	2.38 (s, 3H), 4.43 (m, 2H), 6.01 (s, 2H), 6.15 (m, 2H), 6.90 (m, 1H), 7.03 (m, 1H), 7.14 (m, 1H), 7.30 (m, 1H), 7.92 (m, 2H), 8.01 (m, 1H), 8.84 (s, 1H), 8.96 (s, 1H), 9.20 (s, 1H)
170	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-(2-pyrrolidin-1-ylethyl)benzamide		479.20 (M-H+)	1.70 (m, 4H), 2.53 (m, 4H), 2.60 (m, 2H), 3.28 (m, 2H), 6.01 (s, 2H), 6.14 (s, 1H), 6.90 (m, 1H), 7.01 (m, 1H), 7.12 (m, 1H), 7.27 (m, 1H), 7.86 (s, 1H), 7.91 (m, 1H), 8.00 (m, 1H), 8.20 (s, 1H), 8.96 (s, 1H), 9.16 (s, 1H)
171	3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino]-N-(propan-2-yl carbamoylmethyl) benzamide		483.13 (M+)	1.07 (d, 6H), 3.80 (m, 2H), 3.87 (m, 1H), 6.01 (s, 2H), 6.15 (s, 1H), 6.90 (m, 1H), 7.02 (m, 1H), 7.15 (m, 1H), 7.32 (m, 1H), 7.70 (d, 1H), 7.92 (m, 2H), 8.01 (m, 1H), 8.34 (s, 1H), 8.96 (s, 1H), 9.18 (s, 1H)

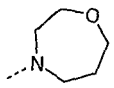
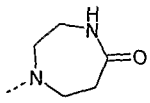
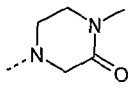
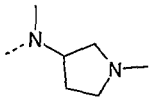
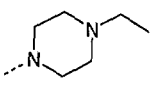
No	Name	R	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)
172	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-[2-(diethylamino)ethyl]benzamide		481.17 (M-H+)	0.99 (m, 6H), 2.54 (m, 6H), 3.28 (m, 2H), 6.01 (s, 2H), 6.15 (s, 1H), 6.90 (m, 1H), 7.03 (m, 1H), 7.14 (m, 1H), 7.25 (m, 1H), 7.87 (s, 1H), 7.90 (m, 1H), 8.00 (m, 1H), 8.10 (s, 1H), 8.96 (s, 1H), 9.17 (s, 1H)
173	{(2S)-1-[3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzoyl]piperidin-2-yl}methanol		482.44 (M+)	
174	1-[3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzoyl]-4-methylpiperidin-4-ol		482.44 (M+)	1.18 (s, 3H), 1.47 (m, 4H), 3.29 (m, 4H), 6.02 (s, 2H), 6.16 (s, 1H), 6.80 (m, 1H), 6.90 (m, 1H), 7.02 (m, 1H), 7.12 (m, 1H), 7.55 (s, 1H), 7.75 (m, 1H), 8.01 (m, 1H), 8.98 (s, 1H), 9.19 (s, 1H)
175	3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino]-N-(dimethylcarbamoylmethyl)-N-methyl-benzamide		483.46 (M+)	

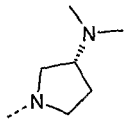
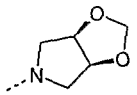
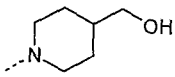
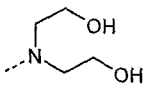
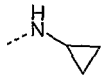
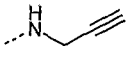
No	Name	R	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)
176	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-methyl-N-(pyridin-3-ylmethyl) benzamide		489.42 (M+)	
177	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-methyl-N-(pyridin-4-ylmethyl) benzamide		489.45 (M+)	
178	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-methyl-N-[(1-methyl-1H-pyrazol-4-yl)methyl] benzamide		492.43 (M+)	
179	N~2~-{3-[(4-acetylpiperazin-1-yl)carbonyl]phenyl}-N~4~-(5-chloro-1,3-benzodioxol-4-yl)pyrimidine-2,4-diamine		495.42 (M+)	2.03 (s, 1H), 3.29 (m, 4H), 3.49 (m, 4H), 6.01 (s, 2H), 6.17 (s, 1H), 6.85 (m, 1H), 6.90 (m, 1H), 7.02 (m, 1H), 7.15 (m, 1H), 7.62 (s, 1H), 7.75 (m, 1H), 8.02 (m, 1H), 8.99 (s, 1H), 9.22 (s, 1H)
181	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-methyl-N-(1-methylpiperidin-4-yl)benzamide		495.52 (M+)	

No	Name	R	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)
182	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-{3-[(4-isopropylpiperazin-1-yl)carbonyl]phenyl}pyrimidine-2,4-diamine		495.49 (M+)	1.00 (d, 6H), 2.46 (m, 4H), 2.70 (m, 1H), 3.33 (m, 4H), 6.01 (s, 2H), 6.17 (s, 1H), 6.81 (m, 1H), 6.90 (m, 1H), 7.02 (m, 1H), 7.13 (m, 1H), 7.58 (s, 1H), 7.76 (m, 1H), 8.01 (m, 1H), 8.99 (s, 1H), 9.20 (s, 1H)
183	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(3-{[4-(dimethylamino)piperidin-1-yl]carbonyl}phenyl)pyrimidine-2,4-diamine		495.48 (M+)	
184	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-(2-hydroxyethyl)-N-methylbenzamide		442.45 (M+)	2.94 (s, 3H), 3.28 (m, 2H), 3.49 (m, 2H), 6.01 (s, 2H), 6.16 (s, 1H), 6.81 (m, 1H), 6.90 (m, 1H), 7.03 (m, 1H), 7.12 (m, 1H), 7.55 (s, 1H), 7.72 (m, 1H), 8.00 (m, 1H), 8.98 (s, 1H), 9.19 (s, 1H)
185	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-[3-(morpholin-4-ylcarbonyl)phenyl]pyrimidine-2,4-diamine		454.44 (M+)	3.33 (m, 4H), 3.61 (m, 4H), 6.02 (s, 2H), 6.18 (s, 1H), 6.84 (m, 1H), 6.90 (m, 1H), 7.02 (m, 1H), 7.14 (m, 1H), 7.51 (s, 1H), 7.76 (m, 1H), 8.02 (m, 1H), 9.00 (s, 1H), 9.22 (s, 1H)

No	Name	R	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)
186	(3R)-1-[3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzoyl]pyrrolidin-3-ol		454.43 (M+)	
187	(3S)-1-[3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzoyl]pyrrolidin-3-ol		454.42 (M+)	
188	1-[3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzoyl]-3-methylazetidin-3-ol		454.43 (M+)	1.39 (s, 1H), 3.38 (m, 2H), 4.08 (m, 2H), 6.01 (s, 2H), 6.17 (s, 1H), 6.90 (m, 1H), 7.03 (m, 1H), 7.07 (m, 1H), 7.13 (m, 1H), 7.75 (s, 1H), 7.90 (m, 1H), 8.01 (m, 1H), 8.99 (s, 1H), 9.22 (s, 1H)
189	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-ethyl-N-(2-hydroxyethyl)benzamide		456.45 (M+)	
190	4-[3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzoyl]piperazin-2-one		467.42 (M+)	

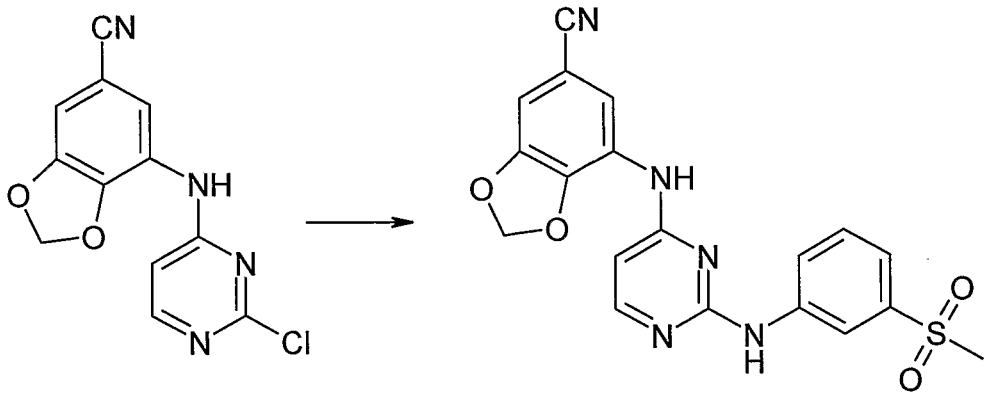
No	Name	R	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)
191	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-{3-[(4-methylpiperazin-1-yl)carbonyl]phenyl}pyrimidine-2,4-diamine		467.45 (M+)	2.20 (s, 3H), 2.32 (m, 4H), 3.33 (m, 4H), 6.01 (s, 2H), 6.16 (s, 1H), 6.80 (m, 1H), 6.90 (m, 1H), 7.03 (m, 1H), 7.12 (m, 1H), 7.56 (s, 1H), 7.75 (m, 1H), 8.01 (m, 1H), 8.98 (s, 1H), 9.20 (s, 1H)
192	{(2S)-1-[3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzoyl]pyrrolidin-2-yl}methanol		468.44 (M+)	
193	1-[3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzoyl]piperidin-4-ol		468.43 (M+)	1.43 (m, 2H), 1.75 (m, 2H), 3.32 (m, 4H), 3.74 (m, 1H), 6.02 (s, 2H), 6.16 (s, 1H), 6.80 (m, 1H), 6.90 (m, 1H), 7.03 (m, 1H), 7.12 (m, 1H), 7.55 (s, 1H), 7.75 (m, 1H), 8.01 (m, 1H), 8.98 (s, 1H), 9.20 (s, 1H)
194	{(2R)-1-[3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzoyl]pyrrolidin-2-yl}methanol		468.43 (M+)	

No	Name	R	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)
195	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-[3-(1,4-oxazepan-4-ylcarbonyl)phenyl]pyrimidine-2,4-diamine		468.44 (M+)	1.71 (m, 1H), 1.88 (m, 1H), 3.33 (M, 4H), 3.70 (m, 4H), 6.01 (s, 2H), 6.16 (s, 1H), 6.80 (m, 1H), 6.90 (m, 1H), 7.03 (m, 1H), 7.13 (m, 1H), 7.59 (s, 1H), 7.72 (m, 1H), 8.02 (m, 1H), 8.99 (s, 1H), 9.22 (s, 1H)
196	1-[3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzoyl]-1,4-diazepan-5-one		481.43 (M+)	
197	4-[3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzoyl]-1-methylpiperazin-2-one		481.42 (M+)	
198	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-methyl-N-(1-methylpyrrolidin-3-yl)benzamide		481.45 (M+)	
199	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-{3-[(4-ethylpiperazin-1-yl)carbonyl]phenyl}pyrimidine-2,4-diamine		481.45 (M+)	1.01 (t, 3H), 2.36 (m, 6H), 3.30 (m, 4H), 6.02 (s, 2H), 6.16 (s, 1H), 6.80 (m, 1H), 6.90 (m, 1H), 7.03 (m, 1H), 7.13 (m, 1H), 7.57 (s, 1H), 7.74 (m, 1H), 8.01 (m, 1H), 8.99 (s, 1H), 9.21 (s, 1H)

No	Name	R	Molecular Ion (Observed)	NMR Spectrum (400 MHz, d6-DMSO)
200	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-(3-{[(3R)-3-(dimethylamino)pyrrolidin-1-yl]carbonyl}phenyl)pyrimidine-2,4-diamine		481.45 (M+)	
201	N~4~-(5-chloro-1,3-benzodioxol-4-yl)-N~2~-{3-[(3aR,6aS)-tetrahydro-5H-[1,3]dioxolo[4,5-c]pyrrol-5-ylcarbonyl]phenyl}pyrimidine-2,4-diamine		481.42 (M+)	3.41 (m, 4H), 4.70 (m, 2H), 4.80 (s, 2H), 6.04 (s, 2H), 6.20 (s, 1H), 6.93 (m, 2H), 7.05 (m, 1H), 7.16 (m, 1H), 7.68 (s, 1H), 7.81 (m, 1H), 8.04 (m, 1H), 9.24 (s, 1H)
202	{1-[3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)benzoyl]piperidin-4-yl}methanol		481.44 (M+)	
204	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N,N-bis(2-hydroxyethyl)benzamide		472.44 (M+)	
205	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-cyclopropyl benzamide		424.44 (M+)	
206	3-({4-[(5-chloro-1,3-benzodioxol-4-yl)amino]pyrimidin-2-yl}amino)-N-prop-2-yn-1-ylbenzamide		422.37 (M+)	

Example 8

7-[(2-{[3-(Methylsulfonyl)phenyl]amino}pyrimidin-4-yl)amino]-1,3-benzodioxole-5-carbonitrile



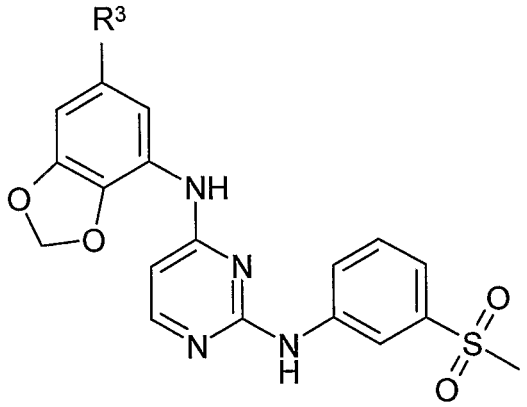
Compound 207

HCl (1 drop, 4N in dioxane) was added to a solution of 7-[(2-chloropyrimidin-4-yl)amino]benzo[1,3]dioxole-5-carbonitrile (83 mg - method 23) and 3-methylsulfonylaniline hydrochloride (69 mg) in iso-propanol (0.5 ml) and NMP (0.5 ml) and heated at 110°C for 20 mins (microwave). The solution was cooled and added DIPEA before concentrating in vacuo. The residue was purified by reverse phase chromatography to give the title compound as a beige solid (21 mg, 17%); NMR Spectrum (300 MHz, DMSO) 3.16 (s, 3H), 6.20 (s, 2H), 6.43 - 6.46 (m, 1H), 7.23 (s, 1H), 7.42 - 7.49 (m, 2H), 7.99 (d, 1H), 8.12 (d, 1H), 8.17 (s, 1H), 8.20 (s, 1H), 9.37 (s, 1H), 9.63 (s, 1H); Mass Spectrum MH^+ 410.33.

Example 9

The procedure described in Example 8 above was repeated using the appropriate chloropyrimidine and aniline. Thus were obtained the compounds described in Table 4 below:

Table 4



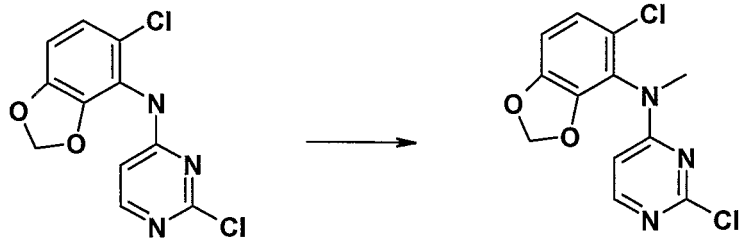
No.	Name	R^3	Molecular Ion (Observed)	NMR Spectrum (300 MHz, d6-DMSO)	Starting Material (method)
208	N~4~-(6-bromo-1,3-benzodioxol-4-yl)-N~2~-[3-(methylsulfonyl)phenyl]pyrimidine-2,4-diamine		465.29 (MH+)		23a
209	N~4~-[6-(2-methoxyethyl)-1,3-benzodioxol-4-yl]-N~2~-[3-(methylsulfonyl) phenyl]pyrimidine-2,4-diamine		443.38 (MH+)		23b

No.	Name	R^3	Molecular Ion (Observed)	NMR Spectrum (300 MHz, d6-DMSO)	Starting Material (method)
210	[7-[[2-[(3-methylsulfonylphenyl)amino]pyrimidin-4-yl]amino]benzo[1,3]dioxol-5-yl]methanol		415.49 (MH+)	3.30 (s, 3H), 4.42 (d, 2H), 5.11 (t, 1H), 6.00 (s, 2H), 6.25 (q, 1H), 6.74 (d, 1H), 7.07 (d, 1H), 7.37 - 7.46 (m, 2H), 8.05 (d, 1H), 8.16 (s, 1H), 8.20 - 8.24 (m, 1H), 9.08 (s, 1H), 9.46 (s, 1H)	24

Example 10

Starting materials

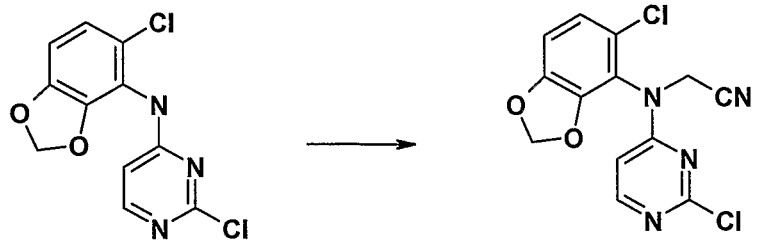
(1) 2-chloro-N-(5-chlorobenzo[1,3]dioxol-4-yl)-N-methyl-pyrimidin-4-amine



2-Chloro-N-(5-chloro-1,3-benzodioxol-4-yl)pyrimidin-4-amine (1.5 g, 5.30 mmol, see Example 1, Step 1) was dissolved in DMF (30 mL). Potassium carbonate (1.1 g, 8.0 mmol) was added, followed by iodomethane (0.36 mL, 5.8 mmol) and the mixture was stirred overnight. After evaporation under reduced pressure, the residue was dissolved in ethyl acetate, washed with water and brine, dried and evaporated to yield a brown oil (1.54 g, 98%) which solidified on standing; NMR Spectrum (500 MHz, DMSOd6 at 353 °K) 3.33

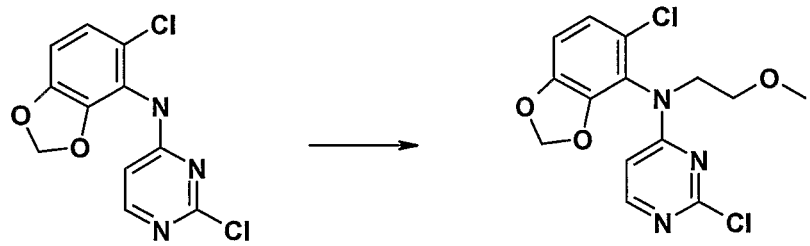
(s, 3H), 6.29 (s, 2H), 7.12 (bs, 1H), 7.00 (d, 1H), 7.10 (d, 1H), 8.12 (bs, 1H); Mass Spectrum MH^+ 298.

(2) (5-chlorobenzo[1,3]dioxol-4-yl)-(2-chloropyrimidin-4-yl)amino]acetonitrile



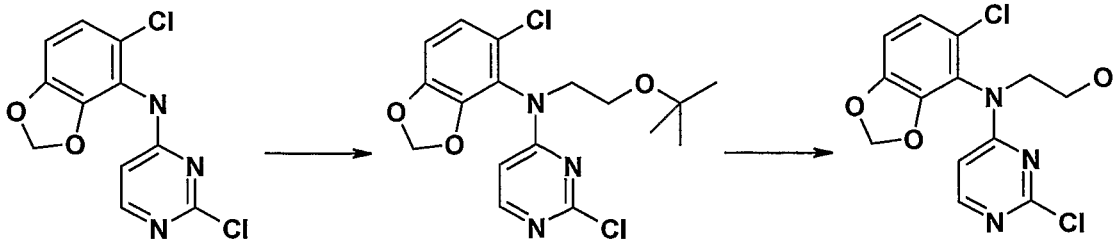
Following the same procedure as for (1) above, 2-chloro-N-(5-chloro-1,3-benzodioxol-4-yl)pyrimidin-4-amine (1.5 g, 5.30 mmol) was reacted with iodoacetonitrile (0.42 mL, 5.8 mmol) to yield a yellow solid (1.53 g, 89%) after trituration in ether/pentane ; NMR Spectrum 4.95 (s, 2H), 6.18 (d, 2H), 6.42 (s, 1H), 7.11 (d, 1H), 7.16 (d, 1H), 8.26 (s, 1H); Mass Spectrum MH^+ 323.

(3) 2-chloro-N-(5-chlorobenzo[1,3]dioxol-4-yl)-N-(2-methoxyethyl)pyrimidin-4-amine



Following the same procedure as for (1) above, 2-chloro-N-(5-chloro-1,3-benzodioxol-4-yl)pyrimidin-4-amine (1.5 g, 5.30 mmol) was reacted with 2-bromoethyl methyl ether (0.55 mL, 5.8 mmol) to yield a brown oil (1.2 g, 67%) ; NMR Spectrum 3.21 (s, 3H), 3.53 (t, 2H), 3.83-3.92 (m, 1H), 4.09-4.19 (m, 1H), 6.13-6.21 (m, 3H), 7.08 (d, 1H), 7.15 (d, 1H), 8.10 (d, 1H); Mass Spectrum MH^+ 342.

(4) 2-[(5-chlorobenzo[1,3]dioxol-4-yl)-(2-chloropyrimidin-4-yl)amino]ethanol

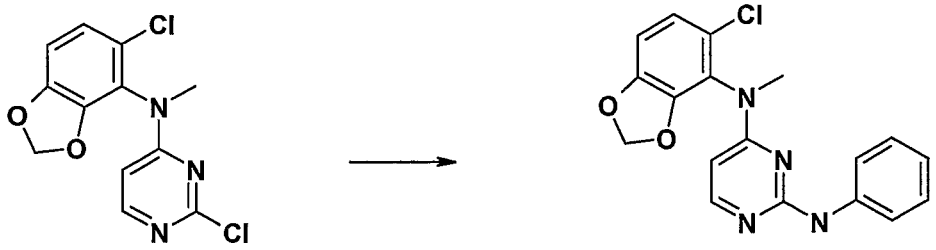


Following the same procedure as for (1) above, 2-chloro-N-(5-chloro-1,3-benzodioxol-4-yl)pyrimidin-4-amine (2.0 g, 7.07 mmol) was reacted with 2-bromoethyl t-butyl ether (1.92 mL, 10.6 mmol) to yield 2-chloro-N-(5-chlorobenzo[1,3]dioxol-4-yl)-N-[2-[(*t*-butyloxy]ethyl]pyrimidin-4-amine as a white solid (2.2 g, 81%) after chromatography on silica gel (EtOAc and petroleum ether, 1:9) ; NMR Spectrum 1.04 (s, 9H), 3.52 (t, 2H), 3.79-3.87 (m, 1H), 3.98-4.04 (m, 1H), 6.13 (s. 2H), 6.16 (d, 1H), 7.05 (d, 1H), 7.12 (d, 1H), 8.09 (d, 1H); Mass Spectrum MH^+ 384.

2-chloro-N-(5-chlorobenzo[1,3]dioxol-4-yl)-N-[2-[(*t*-butyloxy]ethyl]pyrimidin-4-amine (2.1 g) was dissolved in a 1:1 mixture of methylene chloride and TFA (40 mL) and stirred at room temperature for 2 hours. The solvent was then removed and the residue dissolved in ether, washed with aqueous sodium bicarbonate and brine, dried, concentrated and purified by silica gel chromatography (EtOAc and petroleum ether, 3:7) to give the title compound as a white solid (1.06 g, 44%) ; NMR Spectrum (500 MHz, DMSOd6 + TFAd at 297 °K) 3.59 (t, 2H), 3.70-3.78 (m, 1H), 3.99-4.08 (1H, m), 6.12-6.18 (m, 3H), 7.06 (d, 1H), 7.14 (d, 1H), 8.08 (d, 1H); Mass Spectrum MH^+ 328.

Final compounds

N'-(5-chlorobenzo[1,3]dioxol-4-yl)-N'-methyl-N-phenyl-pyrimidine-2,4-diamine

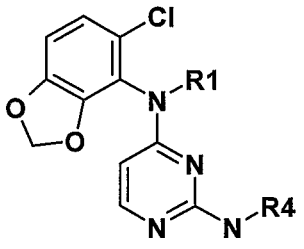


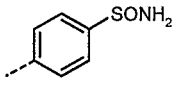
Compound 211

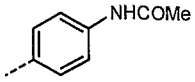
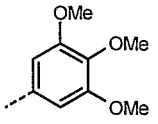
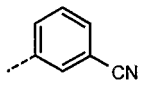
A mixture of 2-chloro-N-(5-chlorobenzo[1,3]dioxol-4-yl)-N-methyl-pyrimidin-4-amine (50 mg, 0.17 mmol), aniline (0.19 mmol), 4N HCl in dioxane (10 uL) and 1-pentanol (1 mL) was heated at 120°C for 1 hour. The reaction mixture was cooled to room temperature, evaporated under reduced pressure and purified on a preparative HPLC-MS system (Column: C18, 5 microns, 19 mm diameter, 100 mm length; elution with a gradient of water and acetonitrile containing 2g/l of ammonium carbonate); evaporation of the collected fractions gave the title compound (65 mg, 61%); NMR Spectrum (500 MHz, DMSOd6 + TFAd) Major rotamer: 3.43 (s, 3H), 5.97 (d, 1H), 6.18 (s, 2H), 7.06-7.22 (m, 2H), 7.24 (t, 1H), 7.46 (t, 2H), 7.62 (d, 2H), 7.92 (d, 1H); Mass Spectrum MH^+ 355.

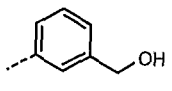
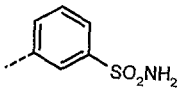
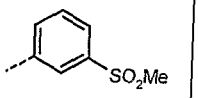
The procedure described above was repeated using the appropriate aniline and 2-chloropyrimidine intermediate. Thus were obtained the compounds described in Table 5 below.

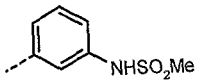
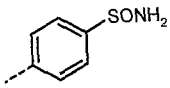
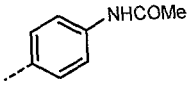
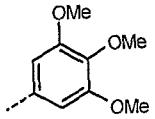
Table 5

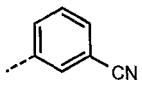
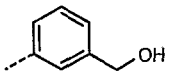
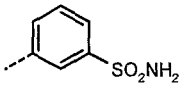


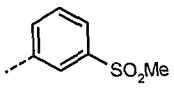
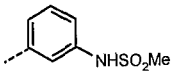
No.	Name	R1	R4	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
212	4-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-methyl-amino]pyrimidin-2-yl]amino] benzenesulfonamide	Me		434	(500 MHz, DMSOd6 + TFAd) Major rotamer: 3.46 (s, 3H), 6.04 (d, 1H), 6.18 (s, 2H), 7.08 (d, 1H), 7.16 (d, 1H), 7.83 (d, 2H), 7.90 (d, 2H), 8.00 (d, 1H)

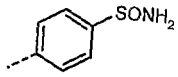
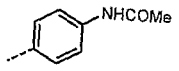
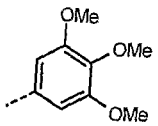
No.	Name	R1	R4	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
213	N-[4-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-methyl-amino]pyrimidin-2-yl]amino]phenyl] acetamide	Me		412	(500 MHz, DMSOd6 + TFAd) Major rotamer: 1.95 (s, 3H), 3.31 (s, 3H), 5.82 (d, 1H), 6.07 (s, 2H), 6.98 (d, 1H), 7.05 (d, 1H), 7.40 (d, 2H), 7.57 (d, 2H), 7.78 (bs, 1H)
214	N'-(5-chlorobenzo[1,3]dioxol-4-yl)-N'-methyl-N-(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine	Me		445	(500 MHz, DMSOd6 at 353 °K) 3.36 (bs, 3H), 3.64 (s, 3H), 3.76 (s, 6H), 5.60 (bs, 1H), 6.12 (s, 2H), 7.00 (d, 1H), 7.10 (d, 1H), 7.21 (bs, 2H), 7.94 (bs, 1H), 8.94 (bs, 1H)
215	3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-methyl-amino]pyrimidin-2-yl]amino]benzonitrile	Me		380	(500 MHz, DMSOd6 + TFAd) Major rotamer: 3.43 (s, 3H), 6.04 (d, 1H), 6.17 (d, 2H), 7.08 (d, 1H), 7.13 (d, 1H), 7.61-7.68 (m, 2H), 7.91 (d, 1H), 7.98 (d, 1H), 8.13 (bs, 1H)

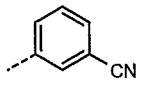
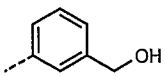
No.	Name	R1	R4	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
216	[3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-methyl-amino]pyrimidin-2-yl]amino]phenyl]methanol	Me		385	(500 MHz, DMSOd6 + TFAd) Major rotamer: 3.34 (s, 3H), 4.54 (s, 2H), 5.94 (d, 1H), 6.15 (s, 2H), 6.97-7.17 (m, 3H), 7.36 (dd, 1H), 7.44 (d, 1H), 7.69 (bs, 1H), 7.91 (d, 1H)
217	3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-methyl-amino]pyrimidin-2-yl]amino] benzenesulfonamide	Me		434	(500 MHz, DMSOd6 + TFAd) Major rotamer: 3.47 (s, 3H), 6.02 (d, 1H), 6.18 (s, 2H), 7.09 (d, 1H), 7.16 (d, 1H), 7.63 (d, 1H), 7.67 (d, 1H), 7.71 (d, 1H), 8.01 (d, 1H), 8.44 (bs, 1H)
218	N'-(5-chlorobenzo[1,3]dioxol-4-yl)-N'-methyl-N-(3-methylsulfonylphenyl) pyrimidine-2,4-diamine	Me		433	(500 MHz, DMSOd6 at 363 °K) 3.14 (s, 3H), 3.41 (s, 3H), 6.03 (bs, 1H), 6.09 (s, 2H), 7.00 (d, 1H), 7.09 (d, 1H), 7.49 (d, 1H), 7.54 (d, 1H), 7.83 (d, 1H), 8.04 (bs, 1H), 8.36 (bs, 1H), 10.20 (bs, 1H)

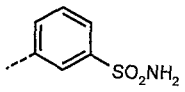
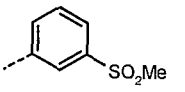
No.	Name	R1	R4	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
219	N-[3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-methyl-amino]pyrimidin-2-yl]amino]phenyl]methane sulfonamide	Me		448	(500 MHz, DMSOd6 + TFAd) Major rotamer: 3.00 (s, 3H), 3.46 (s, 3H), 5.97 (d, 1H), 6.17 (s, 2H), 7.02-7.10 (m, 2H), 7.14 (d, 1H), 7.32 (d, 1H), 7.38 (dd, 1H), 7.60 (bs, 1H), 7.93 (d, 1H)
220	4-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-(cyanomethyl)amino]pyrimidin-2-yl]amino] benzenesulfonamide	CH2CN		459	(500 MHz, DMSOd6 + TFAd) Major rotamer: 5.03 (s, 2H), 6.14 (d, 1H), 6.19 (d, 2H), 6.24 (s, 2H), 7.12 (d, 1H), 6.19 (d, 1H), 7.89 (bs, 4H), 8.18 (d, 1H)
221	N-[4-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-(cyanomethyl)amino] pyrimidin-2-yl]amino] phenyl]acetamide	CH2CN		437	(500 MHz, DMSOd6 + TFAd) Major rotamer: 2.05 (s, 3H), 4.95 (s, 2H), 6.07 (d, 1H), 7.12 (d, 1H), 7.18 (d, 1H), 7.55 (bs, 2H), 7.69 (d, 2H), 8.04 (bs, 1H)
222	2-[(5-chlorobenzo[1,3]dioxol-4-yl)-[2-[(3,4,5-trimethoxyphenyl)amino] pyrimidin-4-yl]amino] acetonitrile	CH2CN		470	(500 MHz, DMSOd6 at 353 °K) 3.65 (s, 3H), 3.77 (s, 6H), 4.86 (d, 2H), 4.95 (d, 1H), 5.77 (d, 1H), 6.11 (s, 2H), 7.02 (d, 1H), 7.10 (d, 1H), 7.11 (s, 2H), 8.05 (d, 1H), 8.90 (s, 1H)

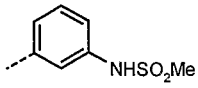
No.	Name	R1	R4	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
223	3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-(cyanomethyl)amino] pyrimidin-2-yl]amino] benzonitrile	CH2CN		405	(500 MHz, DMSOd6 + TFAd) Major rotamer: 4.99 (s, 2H), 6.14 (s, 1H), 6.19 (s, 2H), 7.12 (d, 1H), 7.17 (d, 1H), 7.57-7.69 (m, 2H), 7.95 (s, 1H), 8.15 (d, 1H), 8.19 (s, 1H)
224	2-[(5-chlorobenzo[1,3]dioxol-4-yl)-[2-[[3-(hydroxymethyl)phenyl] amino]pyrimidin-4-yl]amino]acetonitrile	CH2CN		410	(500 MHz, DMSOd6 + TFAd) Major rotamer: 4.56 (s, 2H), 4.97 (s, 2H), 6.10 (d, 1H), 6.18 (d, 2H), 7.09 (d, 1H), 7.15 (d, 1H), 7.21 (d, 1H), 7.39 (dd, 1H), 7.49 (d, 1H), 7.66 (s, 1H), 8.08 (d, 1H)
225	3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-(cyanomethyl)amino] pyrimidin-2-yl]amino] benzenesulfonamide	CH2CN		459	(500 MHz, DMSOd6 + TFAd) Major rotamer: 5.01 (s, 2H), 6.15 (d, 1H), 6.19 (d, 2H), 7.12 (d, 1H), 7.18 (d, 1H), 7.63 (dd, 1H), 7.69 (d, 1H), 7.93 (d, 1H), 8.16 (d, 1H), 8.18 (s, 1H)

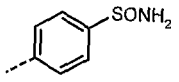
No.	Name	R1	R4	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
226	2-[(5-chlorobenzo[1,3]dioxol-4-yl)-[2-[(3-methylsulfonylphenyl) amino]pyrimidin-4-yl]amino]acetonitrile	CH2CN		458	(500 MHz, DMSOd6 + TFAd) Major rotamer: 3.75 (s, 3H), 5.02 (s, 2H), 6.15 (d, 1H), 6.19 (d, 2H), 7.12 (d, 1H), 7.18 (d, 1H), 7.70 (dd, 1H), 7.76 (d, 1H), 7.94 (d, 1H), 8.17 (d, 1H), 8.47 (s, 1H),
227	N-[3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-(cyanomethyl)amino] pyrimidin-2-yl]amino]phenyl] methanesulfonamide	CH2CN		473	(500 MHz, DMSOd6 + TFAd) Major rotamer: 3.02 (s, 3H), 5.07 (s, 2H), 6.12 (d, 1H), 6.20 (d, 2H), 7.12 (d, 1H), 7.14 (d, 1H), 7.20 (d, 1H), 7.36 (d, 1H), 7.40 (dd, 1H), 7.60 (s, 1H), 8.11 (d, 1H)
228	N'-(5-chlorobenzo[1,3]dioxol-4-yl)-N'-(2-methoxyethyl)-N-phenyl-pyrimidine-2,4-diamine	CH2CH2OMe		399	(500 MHz, DMSOd6 + TFAd) Major rotamer: 3.15 (s, 3H), 3.50-3.60 (m, 2H), 3.83-3.95 (m, 1H), 4.13-4.24 (m, 1H), 6.06 (d, 1H), 6.17 (d, 2H), 7.05-7.19 (m, 2H), 7.23 (t, 1H), 7.43 (dd, 1H), 7.58 (d, 2H), 7.92 (d, 1H), 8.20 (d, 1H)

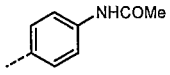
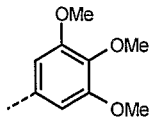
No.	Name	R1	R4	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
229	4-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-(2-methoxyethyl)amino] pyrimidin-2-yl]amino] benzenesulfonamide	CH2CH2OMe		478	(500 MHz, DMSOd6 + TFAd) Major rotamer: 3.20 (s, 3H), 3.55-3.63 (m, 2H), 3.92-4.02 (m, 1H), 4.15-4.28 (m, 1H), 6.00 (d, 1H), 6.19 (d, 2H), 7.10 (d, 1H), 7.12-7.21 (m, 1H), 7.82 (d, 2H), 7.89 (d, 2H), 8.02 (d, 1H)
230	N-[4-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-(2-methoxyethyl)amino] pyrimidin-2-yl]amino] phenyl]acetamide	CH2CH2OMe		456	(500 MHz, DMSOd6 + TFAd) Major rotamer: 2.04 (s, 3H), 3.16 (s, 3H), 3.50-3.58 (m, 2H), 3.84-3.95 (m, 1H), 4.13-4.22 (m, 1H), 5.88 (d, 1H), 6.17 (d, 2H), 7.08 (d, 1H), 7.13 (d, 1H), 7.48 (d, 2H), 7.66 (d, 2H), 7.88 (bs, 1H)
231	N'-(5-chlorobenzo[1,3]dioxol-4-yl)-N'-(2-methoxyethyl)-N-(3,4,5-trimethoxyphenyl) pyrimidine-2,4-diamine	CH2CH2OMe		489	(500 MHz, DMSOd6 at 353 °K): 3.18 (s, 3H), 3.54 (t, 2H), 3.64 (s, 3H), 3.75 (s, 6H), 3.90 (bs, 1H), 5.64 (bs, 1H), 6.08 (s, 2H), 6.95 (d, 1H), 7.06 (d, 1H), 7.10 (s, 2H), 7.91 (d, 1H), 8.67 (s, 1H)

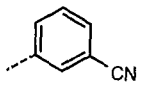
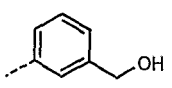
No.	Name	R1	R4	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
232	3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-(2-methoxyethyl)amino] pyrimidin-2-yl]amino]benzonitrile	CH2CH2OMe		424	(500 MHz, DMSOd6 + TFAd) Major rotamer: 3.25 (s, 3H), 3.58-3.66 (m, 2H), 3.97-4.06 (m, 1H), 4.22-4.31 (m, 1H), 6.05 (d, 1H), 6.23 (d, 2H), 7.14 (d, 1H), 7.21 (d, 1H), 7.68 (dd, 1H), 7.71 (d, 1H), 7.87 (ddd, 1H), 8.06 (d, 1H), 8.29 (s, 1H)
233	[3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-(2-methoxyethyl)amino] pyrimidin-2-yl]amino]phenyl]methanol	CH2CH2OMe		429	(500 MHz, DMSOd6 + TFAd) Major rotamer: 3.15 (s, 3H), 3.51-3.60 (m, 2H), 3.91-3.99 (m, 1H), 4.18-4.26 (m, 1H), 4.54 (s, 2H), 5.91 (d, 1H), 6.16 (d, 2H), 7.04-7.10 (m, 1H), 7.13 (d, 1H), 7.17 (d, 1H), 7.37 (d, 1H), 7.41 (d, 1H), 7.64 (s, 1H), 7.93 (d, 1H)

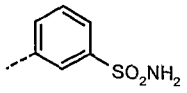
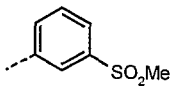
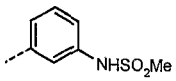
No.	Name	R1	R4	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
234	3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-(2-methoxyethyl)amino] pyrimidin-2-yl]amino]benzenesulfonamide	CH2CH2OMe		478	(500 MHz, DMSOd6 + TFAd) Major rotamer: 3.12 (s, 3H), 3.57 (t, 2H), 3.97-4.04 (m, 1H), 4.19-4.27 (m, 1H), 5.99 (d, 1H), 6.18 (d, 2H), 7.09 (d, 1H), 7.16 (d, 1H), 7.63 (dd, 1H), 7.69 (d, 1H), 7.78 (ddd, 1H), 8.08 (d, 1H), 8.23 (s, 1H)
235	N'-(5-chlorobenzo[1,3]dioxol-4-yl)-N'-(2-methoxyethyl)-N-(3-methylsulfonylphenyl) pyrimidine-2,4-diamine	CH2CH2OMe		477	500 MHz, DMSOd6 + TFAd) Major rotamer: 3.11 (s, 3H), 3.22 (s, 3H), 3.54 (t, 2H), 3.97-4.04 (m, 1H), 4.20-4.28 (m, 1H), 5.98 (d, 1H), 6.15 (d, 2H), 7.05 (d, 1H), 7.12 (d, 1H), 7.69 (dd, 1H), 7.76 (d, 1H), 7.81 (dd, 1H), 8.00 (d, 1H), 8.42 (s, 1H)

No.	Name	R1	R4	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
236	N-[3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-(2-methoxyethyl)amino] pyrimidin-2-yl]amino]phenyl]methane sulfonamide	CH2CH2OMe		492	500 MHz, DMSOd6 + TFAd) Major rotamer: 3.02 (s, 3H), 3.12 (s, 3H), 3.50-3.58 (m, 2H), 3.94-4.02 (m, 1H), 4.19-4.28 (m, 1H), 5.93 (d, 1H), 6.17 (d, 2H), 6.92 (d, 1H), 7.07 (d, 1H), 7.14 (d, 1H), 7.37 (s, 1H), 7.38 (d, 1H), 7.45 (s, 1H), 7.94 (d, 1H)
237	2-[(2-anilinopyrimidin-4-yl)-(5-chlorobenzo[1,3]dioxol-4-yl)amino]ethanol	CH2CH2OH		385	500 MHz, DMSOd6 + TFAd) Two rotamers are seen in the NMR spectrum (nearly 50/50): 3.61-3.71 (m, 2H), 3.74-3.86 (m, 1H), 4.01-4.09 (0.5H), 4.10-4.18 (0.5H), 5.92 (d, 1H), 6.06 (d, 1H), 6.17 (s, 1H), 6.95 (d, 0.5H), 7.02 (dd, 0.5H), 7.06-7.20 (m, 4H), 7.45 (t, 1H), 7.760 (d, 1H), 7.93 (d, 0.5H), 8.22 (d, 0.5H)

No.	Name	R1	R4	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
238	4-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-(2-hydroxyethyl)amino]pyrimidin-2-yl]amino] benzenesulfonamide	CH2CH2OH		464	500 MHz, DMSOd6 + TFAd) Two rotamers are seen in the NMR spectrum (nearly 50/50): 3.65-3.73 (m, 2H), 3.79-3.91 (m, 1H), 4.02-4.11 (m, 0.5H), 4.13-4.22 (m, 0.5H), 5.99 (d, 0.5H), 6.11 (s, 1H), 6.18 (s, 1H), 7.02 (d, 0.5H), 7.09-7.21 (m, 2H), 7.33 (d, 1H), 7.54 (d, 1H), 7.84 (dd, 1H), 7.90 (d, 1H), 8.02 (dd, 1H), 8.29 (dd, 1H)

No.	Name	R1	R4	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
239	N-[4-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-(2-hydroxyethyl)amino] pyrimidin-2-yl]amino] phenyl]acetamide	CH2CH2OH		442	500 MHz, DMSOd6 + TFAd) Two rotamers are seen in the NMR spectrum (nearly 50/50): 2.01 (1.5H), 2.05 (1.5H), 3.60-3.70 (m, 2H), 3.72-3.86 (m, 1H), 4.00-4.08 (m, 0.5H), 4.09-4.17 (m, 0.5H), 5.88 (d, 1H), 6.08 (d, 1H), 6.16 (s, 1H), 6.92 (d, 0.5H), 7.03 (d, 0.5H), 7.06-7.10 (m, 1H), 7.11-7.17 (m, 1H), 7.34 (d, 1H), 7.50 (d, 1H), 7.67 (d, 1H), 7.88 (bs, 0.5H), 8.19 (d, 0.5H)
240	2-[(5-chlorobenzo[1,3]dioxol-4-yl)-[2-[(3,4,5-trimethoxyphenyl)amino] pyrimidin-4-yl]amino]ethanol	CH2CH2OH		475	500 MHz, DMSOd6 at 353 °K) 3.64 (t, 2H), 3.68 (s, 3H), 3.78 (s, 6H), 3.83 (bs, 1H), 4.13 (bs, 1H), 6.09 (bs, 1H), 6.12 (s, 1H), 6.89 (bs, 2H), 7.01 (d, 1H), 7.09 (d, 1H), 7.94 (d, 1H), 10.03 (bs, 1H)

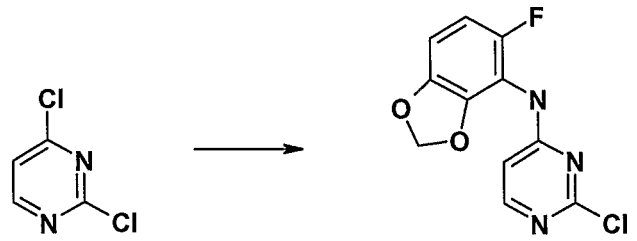
No.	Name	R1	R4	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
241	3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-(2-hydroxyethyl)amino]pyrimidin-2-yl]amino]benzonitrile	CH2CH2OH		410	500 MHz, DMSOd6 + TFAd) Two rotamers are seen in the NMR spectrum (nearly 50/50): 3.63-3.71 (m, 2H), 3.79-3.88 (m, 1H), 3.97-4.06 (m, 0.5H), 4.08-4.17 (m, 0.5H), 5.99 (d, 0.5H), 6.07 (d, 1H), 6.18 (s, 1H), 7.07 (dd, 1H), 7.10 (d, 0.5H), 7.14 (d, 0.5H), 7.16 (d, 0.5H), 7.31 (dd, 0.5H), 7.48 (dd, 1H), 7.54 (bs, 0.5H), 7.61-7.69 (m, 1H), 7.89 (dd, 0.5H), 7.99 (dd, 0.5H), 8.13 (d, 0.5H), 8.28 (dd, 0.5H)
242	2-[(5-chlorobenzo[1,3]dioxol-4-yl)-[2-[[3-(hydroxymethyl)phenyl]amino]pyrimidin-4-yl]amino]ethanol	CH2CH2OH		415	500 MHz, DMSOd6 + TFAd) Major rotamer: 3.67 (t, 2H), 3.78-3.87 (m, 1H), 4.11-4.20 (1H), 4.56 (s, 2H), 5.92 (d, 1H), 6.17 (s, 2H), 7.00 (s, 1H), 7.03-7.21 (m, 3H), 7.33-7.43 (m, 1H), 7.71 (s, 1H), 7.94 (d, 1H)

No.	Name	R1	R4	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
243	3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-(2-hydroxyethyl)amino]pyrimidin-2-yl]amino]benzenesulfonamide	CH2CH2OH		464	500 MHz, DMSOd6 + TFAd) Major rotamer: 3.66 (t, 2H), 3.82-3.91 (m, 1H), 4.12-4.23 (m, 1H), 5.98 (d, 1H), 6.18 (s, 2H), 7.06-7.19 (m, 2H), 7.63 (dd, 1H), 7.67 (d, 1H), 7.76 (d, 1H), 8.02 (d, 1H), 8.28 (bs, 1H)
244	2-[(5-chlorobenzo[1,3]dioxol-4-yl)-[2-[(3-methylsulfonylphenyl)amino]pyrimidin-4-yl]amino]ethanol	CH2CH2OH		463	500 MHz, DMSOd6 at 353 °K) 3.19 (s, 3H), 3.71 (t, 2H), 3.86 (bs, 1H), 4.12 (bs, 1H), 6.13 (s, 2H), 7.05 (d, 1H), 7.14 (d, 1H), 7.52 (bs, 1H), 7.58 (s, 1H), 7.88 (s, 1H), 8.08 (s, 1H), 8.25 (bs, 1H), 10.30 (s, 1H)
245	N-[3-[[4-[(5-chlorobenzo[1,3]dioxol-4-yl)-(2-hydroxyethyl)amino]pyrimidin-2-yl]amino]phenyl]methanesulfonamide	CH2CH2OH		478	500 MHz, DMSOd6 + TFAd) 3.03 (s, 3H), 3.65 (t, 2H), 3.82-3.91 (m, 1H), 4.12-4.21 (m, 1H), 5.93 (d, 1H), 6.17 (s, 2H), 6.93 (d, 1H), 6.86-7.17 (m, 3H), 7.35-7.42 (m, 2H), 7.47 (s, 1H),

Example 11

Starting material

2-chloro-N-(5-fluorobenzo[1,3]dioxol-4-yl)pyrimidin-4-amine

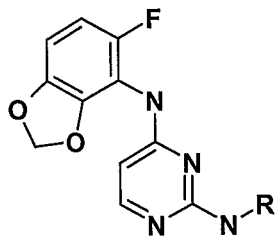


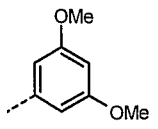
The title compound was prepared from 5-fluorobenzo[1,3]dioxol-4-amine following the procedure described in Example 1, Step 1, except that THF was used as a solvent (30% yield); NMR Spectrum 6.09 (s, 2H), 6.62 (br s, 1H), 6.79 (dd, 1H), 6.87 (dd, 1H), 8.16 (d, 1H), 9.77 (br s, 1H) ; Mass Spectrum MH^+ 268.

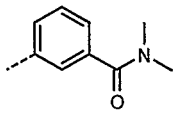
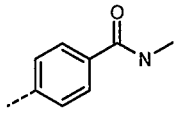
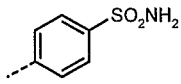
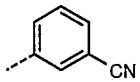
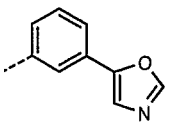
Final compounds

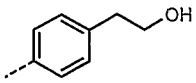
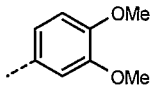
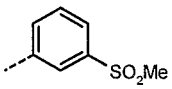
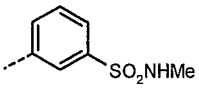
The procedure described in Example 10 (Final compounds) was repeated using the appropriate aniline and 2-chloro-N-(5-fluorobenzo[1,3]dioxol-4-yl)pyrimidin-4-amine. Thus were obtained the compounds described in Table 6 below.

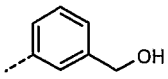
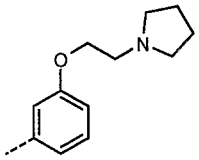
Table 6



No.	Name	R	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
246	N-(3,5-dimethoxyphenyl)-N'-(5-fluorobenzo[1,3]dioxol-4-yl)pyrimidine-2,4-diamine		385	3.61 (s, 6H), 6.01 (s, 2H), 6.02 (t, 1H), 6.13 (d, 1H), 6.74 (dd, 1H), 6.81 (dd, 1H), 6.95 (d, 2H), 8.01 (d, 1H), 8.96 (s, 1H), 9.00 (s, 1H).

No.	Name	R	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
247	3-[[4-[(5-fluorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino]-N,N-dimethyl-benzamide		396	2.84 (s, 3H), 2.98 (s, 3H), 6.02 (s, 2H), 6.17 (d, 1H), 6.75 (dd, 1H), 6.78-6.90 (m, 2H), 7.14 (dd, 1H), 7.62 (s, 1H), 7.70 (d, 1H), 8.02 (d, 1H), 9.02 (bs, 1H), 9.25 (s, 1H).
248	4-[[4-[(5-fluorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino]-N-methyl-benzamide		382	2.76 (d, 3H), 6.03 (s, 2H), 6.20 (d, 1H), 6.81 (dd, 1H), 6.89 (dd, 1H), 7.59 (d, 2H), 7.68 (d, 2H), 8.05 (d, 1H), 8.18 (q, 1H), 9.09 (s, 1H), 9.41 (s, 1H).
249	4-[[4-[(5-fluorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino]benzenesulfonamide		404	6.05 (s, 2H), 6.24 (d, 1H), 6.81 (dd, 1H), 6.90 (dd, 1H), 7.12 (s, 2H), 7.54 (d, 2H), 7.77 (d, 2H), 8.07 (d, 1H), 9.14 (s, 1H), 9.58 (s, 1H).
250	3-[[4-[(5-fluorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino]benzonitrile		350	6.02 (s, 2H), 6.22 (d, 1H), 6.77-6.87 (m, 2H), 7.27 (d, 1H), 7.33 (dd, 1H), 7.86 (d, 1H), 8.06 (d, 1H), 8.11 (bs, 1H), 9.15 (s, 1H), 9.52 (s, 1H).
251	N'-(5-fluorobenzo[1,3]dioxol-4-yl)-N-(3-1,3-oxazol-5-ylphenyl)pyrimidine-2,4-diamine		392	5.97 (s, 2H), 6.17 (d, 1H), 6.72-6.82 (m, 2H), 7.19-7.24 (m, 2H), 7.48 (s, 1H), 7.70 (dd, 1H), 7.96 (bs, 1H), 8.04 (d, 1H), 8.39 (s, 1H), 9.03 (bs, 1H), 9.27 (s, 1H).

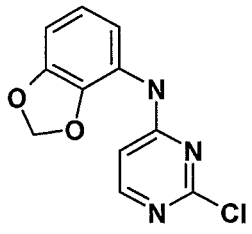
No.	Name	R	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
252	2-[4-[[4-[(5-fluorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino]phenyl]ethanol		369	2.61 (t, 2H), 3.49-3.56 (m, 2H), 4.58 (t, 1H), 6.01 (s, 2H), 6.11 (d, 1H), 6.78 (dd, 1H), 6.86 (dd, 1H), 6.94 (d, 1H), 6.95 (s, 1H), 7.51 (d, 1H), 7.98 (d, 1H), 8.95 (s, 1H), 9.00 (s. 1H).
253	N-(3,4-dimethoxyphenyl)-N'-(5-fluorobenzo[1,3]dioxol-4-yl)pyrimidine-2,4-diamine		385	3.56 (s, 3H), 3.68 (s, 3H), 5.98 (s, 2H), 6.08 (d, 1H), 6.70 (d, 1H), 6.77 (dd, 1H), 6.83 (dd, 1H), 7.18 (dd, 1H), 7.29 (bs, 1H), 7.97 (d, 1H), 8.87 (bs, 1H), 8.91 (bs, 1H).
254	N'-(5-fluorobenzo[1,3]dioxol-4-yl)-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine		403	3.13 (s, 3H), 6.05 (s, 2H), 6.21 (d, 1H), 6.79 (dd, 1H), 6.86 (dd, 1H), 7.32-7.40 (m, 2H), 8.06 (d, 1H), 8.09-8.15 (m, 2H), 9.08 (bs, 1H), 9.51 (s, 1H).
255	3-[[4-[(5-fluorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino]-N-methyl-benzenesulfonamide		418	2.42 (s, 3H), 6.04 (s, 2H), 6.19 (d, 1H), 6.79 (dd, 1H), 6.86 (dd, 1H), 7.24 (d, 1H), 7.30 (dd, 1H), 7.37 (bs, 1H), 8.00 (s, 1H), 8.05 (d, 1H), 8.08 (d, 1H), 9.04 (bs, 1H), 9.46 (s, 1H).

No.	Name	R	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
256	[3-[[4-[(5-fluorobenzo[1,3]dioxol-4-yl)amino]pyrimidin-2-yl]amino]phenyl]methanol		355	4.37 (s, 2H), 5.01 (bs, 1H), 6.00 (s, 2H), 6.13 (d, 1H), 6.78 (dd, 1H), 6.81-6.87 (m, 2H), 7.05 (dd, 1H), 7.48 (s, 1H), 7.93 (bs, 1H), 8.95 (bs, 1H), 9.08 (s, 1H).
257	N'-(5-fluorobenzo[1,3]dioxol-4-yl)-N-[3-(2-pyrrolidin-1-ylethoxy)phenyl]pyrimidine-2,4-diamine		438	1.63-1.75 (m, 4H), 2.48-2.52 (m partially hidden by DMSO-d5, 4H), 2.75 (t, 2H), 3.93 (t, 2H), 6.01 (s, 2H), 6.14 (d, 1H), 6.43 (dd, 1H), 6.77 (dd, 1H), 6.82 (dd, 1H), 6.99 (dd, 1H), 7.24 (d, 1H), 7.27 (s, 1H), 8.01 (d, 1H), 8.98 (s, 1H), 9.04 (s, 1H).

Example 12

Starting material

N-benzo[1,3]dioxol-4-yl-2-chloro-pyrimidin-4-amine



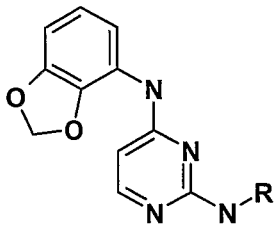
A mixture of 2,4-dichloropyrimidine (4.0 g, 27 mmol), 4-aminobenzodioxole (3.7 g, 27 mmol) and diethylisopropylamine (5.1 ml, 29.7 mmol) in DMF (25 ml) was stirred at 50°C for 18 hours, then at 80°C for 9 hours. After concentration under vacuum, the residue was partitioned between water and ethyl acetate and the precipitate was filtered, washed with water then ether and dried under vacuum. The organic layer from the filtrate was dried,

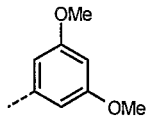
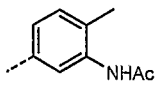
evaporated and the residue purified on silica gel (10 to 50% EtOAc in petroleum ether) to give a solid, which was combined with the precipitate to provide 3.35 g of the title compound (50% yield); NMR Spectrum 6.05 (s, 2H), 6.68 (br s, 1H), 6.81 (d, 1H), 6.87 (t, 1H), 7.05 (br s, 1H), 8.15 (d, 1H), 9.83 (br s, 1H) ; Mass Spectrum MH^+ 250.

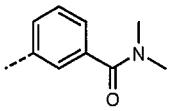
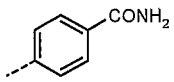
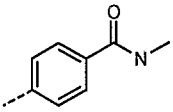
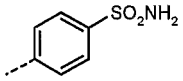
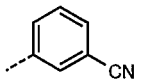
Final compounds

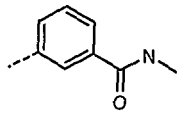
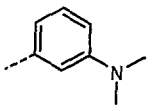
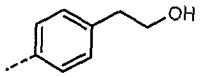
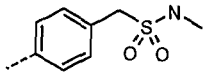
The procedure described in Example 10 (Final compounds) was repeated using N-benzo[1,3]dioxol-4-yl-2-chloro-pyrimidin-4-amine and the appropriate aniline. Thus were obtained the compounds described in Table 7 below.

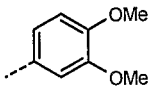
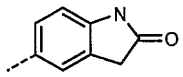
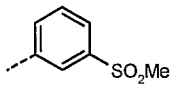
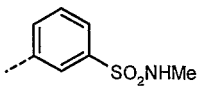
Table 7

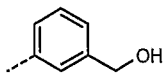
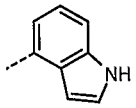
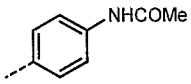


No.	Name	R	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
258	N'-benzo[1,3]dioxol-4-yl-N-(3,5-dimethoxyphenyl)pyrimidine-2,4-diamine		367	3.65 (s, 6H), 5.98 (s, 2H), 6.31 (s, 1H), 6.49 (bs, 1H), 6.69 (d, 2H), 6.82-6.91 (m, 2H), 7.06 (d, 1H), 8.01 (d, 1H), 10.57 (bs, 1H), 10.72 (bs, 1H)
259	N-[5-[[4-(benzo[1,3]dioxol-4-ylamino)pyrimidin-2-yl]amino]-2-methyl-phenyl]acetamide		378	2.07 (s, 3H), 2.17 (s, 3H), 6.02 (s, 2H), 6.49 (bs, 1H), 6.84-6.93 (m, 2H), 7.03-7.16 (m, 2H), 7.28 (bs, 1H), 7.53 (s, 1H), 7.99 (d, 1H), 9.30 (s, 1H), 10.56 (bs, 1H), 10.74 (bs, 1H).

No.	Name	R	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
260	3-[[4-(benzo[1,3]dioxol-4-ylamino)pyrimidin-2-yl]amino]-N,N-dimethyl-benzamide		378	2.86 (s, 3H), 2.96 (s, 3H), 6.01 (s, 2H), 6.26 (d, 1H), 6.75 (d, 1H), 6.82 (dd, 1H), 6.86 (d, 1H), 7.21 (d, 1H), 7.24 (d, 1H), 7.75 (d, 1H), 7.77 (d, 1H), 8.02 (d, 1H), 9.08 (s, 1H), 9.26 (s, 1H).
261	4-[[4-(benzo[1,3]dioxol-4-ylamino)pyrimidin-2-yl]amino]benzamide		350	-
262	4-[[4-(benzo[1,3]dioxol-4-ylamino)pyrimidin-2-yl]amino]-N-methyl-benzamide		364	2.79 (d, 3H), 6.02 (s, 2H), 6.51 (d, 1H), 6.73 (d, 1H), 6.93 (d, 1H), 7.04 (dd, 1H), 7.59 (d, 2H), 7.75 (d, 2H), 8.07 (d, 1H), 8.27 (q, 1H), 10.67 (s, 1H), 10.73 (s, 1H).
263	4-[[4-(benzo[1,3]dioxol-4-ylamino)pyrimidin-2-yl]amino]benzenesulfonamide		386	6.03 (s, 2H), 6.55 (d, 1H), 6.72 (d, 2H), 6.88 (dd, 1H), 6.94 (d, 1H), 7.03 (dd, 1H), 7.23 (bs, 2H), 7.53 (d, 2H), 8.11 (d, 1H), 10.84 (s, 1H), 11.08 (s, 1H).
264	3-[[4-(benzo[1,3]dioxol-4-ylamino)pyrimidin-2-yl]amino]benzonitrile		332	5.99 (s, 2H), 6.51 (d, 1H), 6.87 (dd, 1H), 6.92 (dd, 1H), 7.05 (dd, 1H), 7.48 (dd, 1H), 7.53 (ddd, 1H), 7.77 (ddd, 1H), 8.03 (bs, 1H), 8.08 (d, 1H), 10.57 (bs, 1H), 10.78 (bs, 1H).

No.	Name	R	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
265	3-[[4-(benzo[1,3]dioxol-4-ylamino)pyrimidin-2-yl]amino]-N-methyl-benzamide		364	2.76 (d, 3H), 6.01 (s, 2H), 6.27 (d, 1H), 6.73 (dd, 1H), 6.80 (dd, 1H), 7.24 (dd, 1H), 7.29 (ddd, 1H), 7.34 (d, 1H), 7.93 (ddd, 1H), 8.01 (bs, 1H), 8.02 (d, 1H), 8.25 (q, 1H), 9.05 (s, 1H), 9.23 (s, 1H).
266	N'-benzo[1,3]dioxol-4-yl-N-(3-dimethylaminophenyl)pyrimidine-2,4-diamine		350	2.96 (s, 6H), 6.05 (s, 2H), 6.66 (dd, 1H), 6.68 (d, 1H), 6.74 (dd, 1H), 6.79 (dd, 1H), 6.80 (dd, 1H), 6.88 (dd, 1H), 7.03(bs, 1H), 7.08 (d, 1H), 7.27 (dd, 1H), 8.14 (d, 1H), 9.74 (bs, 1H).
267	2-[4-[[4-(benzo[1,3]dioxol-4-ylamino)pyrimidin-2-yl]amino]phenyl]ethanol		351	2.64 (t, 2H), 3.55 (td, 2H), 4.60 (t, 1H), 6.00 (s, 2H), 6.20 (d, 1H), 6.75 (dd, 1H), 6.83 (dd, 1H), 7.01 (d, 2H), 7.27 (d, 1H), 7.59 (d, 2H), 7.98 (d, 1H), 9.00 (s, 1H), 9.01 (s, 1H).
268	1-[4-[[4-(benzo[1,3]dioxol-4-ylamino)pyrimidin-2-yl]amino]phenyl]-N-methyl-methanesulfonamide		414	2.56 (d, 3H), 4.23 (s, 2H), 6.03 (s, 2H), 6.25 (d, 1H), 6.78 (dd, 1H), 6.84 (q, 1H), 6.86 (dd, 1H), 7.18 (d, 2H), 7.26 (d, 1H), 7.73 (d, 2H), 8.02 (d, 1H), 9.09 (s, 1H), 9.21 (s, 1H).

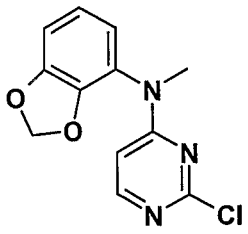
No.	Name	R	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
269	N'-benzo[1,3]dioxol-4-yl-N-(3,4-dimethoxyphenyl)pyrimidine-2,4-diamine		367	(500 MHz, DMSOd6 at 323 °K) 3.63 (s, 3H), 3.77 (s, 3H), 5.97 (s, 2H), 6.44 (d, 1H), 6.81-6.88 (m, 2H), 6.91 (d, 1H), 6.97 (dd, 1H), 7.05-7.12 (m, 2H), 7.94 (d, 1H), 10.26 (bs, 1H), 10.47 (bs, 1H).
270	5-[[4-(benzo[1,3]dioxol-4-ylamino)pyrimidin-2-yl]amino]-1,3-dihydroindol-2-one		362	3.32 (s, 2H), 5.99 (s, 2H), 6.17 (d, 1H), 6.63 (d, 1H), 6.77 (dd, 1H), 6.84 (dd, 1H), 7.20 (d, 1H), 7.37 (dd, 1H), 7.67 (s, 1H), 7.96 (d, 1H), 8.96 (s, 1H), 9.00 (s, 1H), 10.16 (s, 1H)
271	N'-benzo[1,3]dioxol-4-yl-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine		385	3.15 (s, 3H), 6.03 (s, 2H), 6.31 (d, 1H), 6.76 (dd, 1H), 6.86 (dd, 1H), 7.29 (d, 1H), 7.41 (ddd, 1H), 7.44 (dd, 1H), 8.06 (d, 1H), 8.18 (ddd, 1H), 8.22 (bs, 1H), 9.14 (s, 1H), 9.52 (s, 1H).
272	3-[[4-(benzo[1,3]dioxol-4-ylamino)pyrimidin-2-yl]amino]-N-methyl-benzenesulfonamide		400	(500 MHz, DMSOd6 at 323°K) 2.44 (d, 3H), 6.00 (s, 2H), 6.49 (d, 1H), 6.84-6.91 (m, 2H), 7.06 (dd, 1H), 7.40 (bs, 1H), 7.46 (dd, 1H), 7.51 (ddd, 1H), 7.80 (bs, 1H), 7.96 (d, 1H), 8.06 (d, 1H), 10.44 (bs, 1H), 10.60 (bs, 1H),

No.	Name	R	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
273	[3-[[4-(benzo[1,3]dioxol-4-ylamino)pyrimidin-2-yl]amino]phenyl]methanol		337	4.39 (d, 2H), 5.07 (t, 1H), 6.00 (s, 2H), 6.23 (d, 1H), 6.74 (dd, 1H), 6.84 (dd, 1H), 6.86 (d, 1H), 7.12 (dd, 1H), 7.31 (d, 1H), 7.60 (d, 1H), 7.61 (s, 1H), 8.00 (d, 1H), 9.03 (s, 1H), 9.08 (s, 1H).
274	N'-benzo[1,3]dioxol-4-yl-N-(1H-indol-4-yl)pyrimidine-2,4-diamine		346	(500 MHz, DMSOd6 at 323 °K) 6.00 (s, 2H), 6.49 (bs, 1H), 6.67 (s, 1H), 6.80-6.91 (m, 2H), 6.94-7.10 (m, 2H), 7.29 (d, 1H), 7.33-7.41 (m, 2H), 8.00 (d, 1H), 10.42 (s, 1H), 10.63 (s, 1H), 11.22 (s, 1H).
275	N-[4-[[4-(benzo[1,3]dioxol-4-ylamino)pyrimidin-2-yl]amino]phenyl]acetamide		364	2.00 (s, 3H), 6.01 (s, 2H), 6.20 (d, 1H), 6.75 (dd, 1H), 6.83 (dd, 1H), 7.25 (d, 1H), 7.37 (d, 2H), 7.60 (d, 2H), 7.98 (d, 1H), 9.02 (s, 1H), 9.03 (s, 1H), 9.75 (s, 1H).

Example 13

Starting material

N-benzo[1,3]dioxol-4-yl-2-chloro-N-methyl-pyrimidin-4-amine



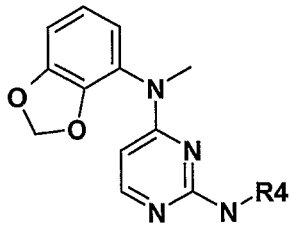
The title compound was prepared following the same procedure as for Example 10 (starting material (1)) except that caesium carbonate was used as a base (68% yield); NMR

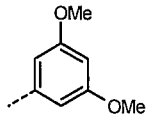
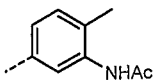
Spectrum 3.36 (s, 3H), 6.06 (s, 2H), 6.41 (br s, 1H), 6.88-6.91 (m, 1H), 6.94-6.98 (m, 2H), 8.07 (d, 1H); Mass Spectrum MH^+ 264.

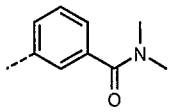
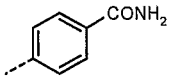
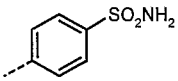
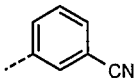
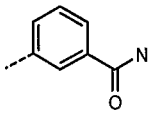
Final compounds

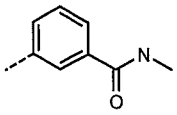
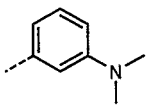
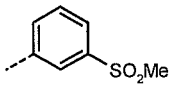
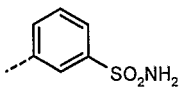
The procedure described in Example 10 (Final compounds) was repeated using N-benzo[1,3]dioxol-4-yl-2-chloro-N-methyl-pyrimidin-4-amine and the appropriate aniline. Thus were obtained the compounds described in Table 8 below.

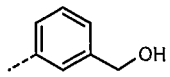
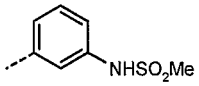
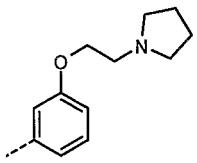
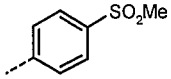
Table 8

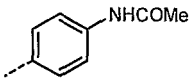


No.	Name	R4	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
276	N'-benzo[1,3]dioxol-4-yl-N-(3,5-dimethoxyphenyl)-N'-methyl-pyrimidine-2,4-diamine		381	3.41 (s, 3H), 3.69 (s, 6H), 5.85 (s, 1H), 6.04 (s, 2H), 6.07 (t, 1H), 6.88 (dd, 1H), 6.91-6.97 (m, 2H), 7.07 (d, 2H), 7.93 (d, 1H), 9.14 (s, 1H).
277	N-[5-[[4-(benzo[1,3]dioxol-4-yl-methyl-amino)pyrimidin-2-yl]amino]-2-methyl-phenyl]acetamide		392	2.03 (s, 3H), 2.10 (s, 3H), 3.37 (s, partially hidden by H2O, 3H), 5.86 (d, 1H), 6.03 (s, 2H), 6.84-6.89 (m, 1H), 6.93 (d, 1H), 6.94 (s, 1H), 6.99 (d, 1H), 7.44 (dd, 1H), 7.73 (bs, 1H), 7.92 (d, 1H), 9.10 (s, 1H), 9.23 (s, 1H).

No.	Name	R4	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
278	3-[[4-(benzo[1,3]dioxol-4-yl-methyl-amino)pyrimidin-2-yl]amino]-N,N-dimethyl-benzamide		392	2.90 (s, 3H), 2.98 (s, 3H), 3.38 (s, 3H), 5.94 (d, 1H), 6.02 (s, 2H), 6.84-6.90 (m, 2H), 6.91-6.98 (m, 2H), 7.22 (dd, 1H), 7.75 (s, 1H), 7.76 (d, 1H), 7.97 (d, 1H), 9.33 (s, 1H).
279	4-[[4-(benzo[1,3]dioxol-4-yl-methyl-amino)pyrimidin-2-yl]amino]benzamide		364	3.40 (s, 3H), 6.00 (bs, 1H), 6.03 (s, 2H), 6.89 (dd, 1H), 6.95-6.99 (m, 2H), 7.11 (bs, 1H), 7.68-7.79 (s, 5H), 8.01 (d, 1H), 9.48 (s, 1H).
280	4-[[4-(benzo[1,3]dioxol-4-yl-methyl-amino)pyrimidin-2-yl]amino]benzenesulfonamide		400	3.40 (s, 3H), 6.03 (s, 2H), 6.05 (bs, 1H), 6.89 (dd, 1H), 6.95-6.99 (m, 2H), 7.13 (bs, 2H), 7.61 (d, 2H), 7.81 (d, 2H), 8.03 (d, 1H), 9.62 (s, 1H).
281	3-[[4-(benzo[1,3]dioxol-4-yl-methyl-amino)pyrimidin-2-yl]amino]benzonitrile		346	3.39 (s, 3H), 6.01 (bs, 1H), 6.02 (s, 2H), 6.89 (dd, 1H), 6.93-6.98 (m, 2H), 7.30 (d, 1H), 7.38 (dd, 1H), 7.94 (d, 1H), 8.02 (d, 1H), 8.18 (bs, 1H), 9.59 (s, 1H).
282	3-[[4-(benzo[1,3]dioxol-4-yl-methyl-amino)pyrimidin-2-yl]amino]benzamide		364	3.42 (s, 3H), 5.91 (d, 1H), 6.05 (s, 2H), 6.86-6.92 (m, 1H), 6.96 (d, 2H), 7.20-7.31 (m, 2H), 7.38 (d, 1H), 7.80-7.88 (m, 2H), 7.97 (d, 1H), 8.28 (bs, 1H), 9.32 (s, 1H).

No.	Name	R4	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
283	3-[[4-(benzo[1,3]dioxol-4-yl-methyl-amino)pyrimidin-2-yl]amino]-N-methyl-benzamide		378	2.77 (d, 3H), 3.41 (s, 3H), 5.90 (d, 1H), 6.03 (s, 2H), 6.86-6.90 (m, 1H), 6.92-6.97 (m, 2H), 7.24 (dd, 1H), 7.30 (d, 1H), 7.80 (dd, 1H), 7.95 (d, 1H), 8.26 (bs, 1H), 8.29 (q, 1H), 9.33 (s, 1H).
284	N'-benzo[1,3]dioxol-4-yl-N-(3-dimethylaminophenyl)-N'-methyl-pyrimidine-2,4-diamine		364	2.86 (s, 6H), 3.40 (s, 3H), 5.83 (d, 1H), 6.03 (s, 2H), 6.30 (dd, 1H), 6.87 (dd, 1H), 6.91-6.96 (m, 2H), 6.99 (dd, 1H), 7.08 (d, 1H), 7.21 (s, 1H), 7.92 (d, 1H), 8.94 (s, 1H).
285	N'-benzo[1,3]dioxol-4-yl-N'-methyl-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine		399	3.1 7 (s, 3H), 3.43 (s, 3H), 5.93 (d, 1H), 6.05 (s, 2H), 6.89 (dd, 1H), 6.92-6.99 (m, 2H), 7.42 (d, 1H), 7.47 (dd, 1H), 7.89 (d, 1H), 7.98 (d, 1H), 8.62 (bs, 1H), 9.67 (s, 1H).
286	3-[[4-(benzo[1,3]dioxol-4-yl-methyl-amino)pyrimidin-2-yl]amino]benzenesulfonamide		400	3.42 (s, 3H), 5.91 (d, 1H), 6.05 (s, 2H), 6.86-6.91 (m, 1H), 6.93-6.99 (m, 2H), 7.26 (s, 2H), 7.32-7.41 (m, 2H), 7.79 (d, 1H), 7.97 (d, 1H), 8.50 (bs, 1H), 9.57 (s, 1H).

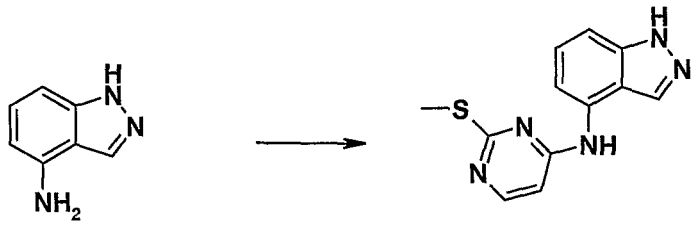
No.	Name	R4	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
287	[3-[[4-(benzo[1,3]dioxol-4-yl-methyl-amino)pyrimidin-2-yl]amino]phenyl]methanol		351	3.39 (s, 3H), 4.42 (d, 2H), 5.10 (t, 1H), 5.89 (d, 1H), 6.02 (s, 2H), 6.84 (d, 1H), 6.86-6.90 (m, 1H), 6.92-6.97 (m, 2H), 7.13 (dd, 1H), 7.55 (d, 1H), 7.72 (bs, 1H), 7.95 (d, 1H), 9.15 (s, 1H).
288	N-[3-[[4-(benzo[1,3]dioxol-4-yl-methyl-amino)pyrimidin-2-yl]amino]phenyl]methanesulfonamide		414	3.40 (s, 3H), 5.87 (d, 1H), 6.04 (s, 2H), 6.74 (dd, 1H), 6.84-6.90 (m, 1H), 6.92-6.97 (m, 2H), 7.13 (dd, 1H), 7.47 (dd, 1H), 7.66 (s, 1H), 7.93 (d, 1H), 9.24 (s, 1H), 9.59 (s, 1H).
289	N'-benzo[1,3]dioxol-4-yl-N'-methyl-N-[3-(2-pyrrolidin-1-ylethoxy)phenyl]pyrimidine-2,4-diamine		434	1.62-1.73 (m, 4H), 2.51-2.63 (m, partially hidden by H2O, 4H) 2.77 (t, 2H), 3.39 (s, 3H), 4.00 (t, 2H), 5.89 (d, 1H), 6.03 (s, 2H), 6.46 (dd, 1H), 6.85-6.90 (m, 1H), 6.92-6.97 (m, 2H), 7.07 (dd, 1H), 7.27 (dd, 1H), 7.49 (bs, 1H), 7.95 (d, 1H, 9.15 (s, 1H).
290	N'-benzo[1,3]dioxol-4-yl-N'-methyl-N-(4-methylsulfonylphenyl)pyrimidine-2,4-diamine		399	3.13 (s, 3H), 3.41 (s, 3H), 6.03 (s, 2H), 6.07 (bs, 1H), 6.90 (dd, 1H), 6.94-7.01 (m, 2H), 7.69 (d, 2H), 7.91 (d, 2H), 8.04 (d, 1H), 9.78 (s, 1H).

No.	Name	R4	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
291	N-[4-[[4-(benzo[1,3]dioxol-4-yl-methyl-amino)pyrimidin-2-yl]amino]phenyl]acetamide		378	2.00 (s, 3H), 3.38 (s, partially hidden by H2O, 3H), 5.91 (d, 1H), 6.01 (s, 2H), 6.84-6.89 (m, 1H), 6.90-6.97(m, 2H), 7.37 (d, 2H), 7.56 (d, 2H), 7.94 (d, 1H), 9.08 (s, 1H), 9.75 (s, 1H).

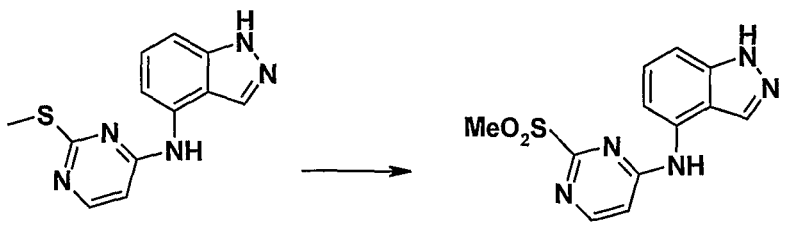
Example 14

Starting material

N-(2-methylsulfonylpyrimidin-4-yl)-1H-indazol-4-amine



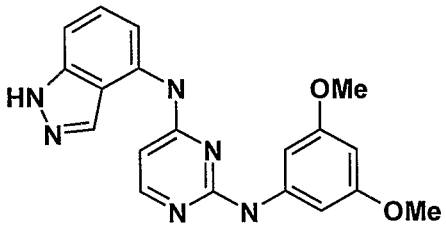
A mixture of 4-chloro-2-methylthiopyrimidine (2.75 ml, 23.7 mmol) and 4-aminoindazole (3.0 g, 22.5 mmol) and hydrogen chloride (1 drop, 4N in dioxane) in n-butanol (45 ml) was heated at 80°C for 4 hours. Diethyl ether was added and the resulting precipitate was filtered and rinsed with ether. This solid was taken in water, the pH adjusted to 7 by addition of aqueous sodium bicarbonate and the solid was filtered and rinsed with water, ether and dried under vacuum to yield 5.7 g (93%) of a pale yellow solid. NMR Spectrum: (500 MHz, DMSO) 2.46 (s, 3H), 6.69 (d, 1H), 7.23 (d, 1H), 7.31 (t, 1H), 7.71 (d, 1H), 8.16 (d, 1H), 8.23 (s, 1H), 9.71 (s, 1H), 13.1 (br s, 1H); Mass spectrum: MH^+ 258.



m-Chloroperbenzoic acid (6.81 g, 27.7 mmol) was added to an ice-cooled solution of N-(2-methylsulfanylpyrimidin-4-yl)-1H-indazol-4-amine (3 g, 11.6 mmol) in DMF (80 ml). The mixture was then stirred at room temperature for 3 hours. The mixture was concentrated, diluted in DCM, washed with sodium bicarbonate and brine, and dried over $MgSO_4$. After evaporation of the solvents, the residue was triturated in EtOAc/ether and dried to give N-(2-methylsulfonylpyrimidin-4-yl)-1H-indazol-4-amine (2.4 g, 71%) as a solid. NMR Spectrum: (500 MHz, DMSO) 3.31 (s, 3H), 7.13 (d, 1H), 7.32-7.38 (m, 2H), 7.66 (br s, 1H), 8.23 (s, 1H), 8.47 (d, 1H), 10.3 (br s, 1H), 13.1 (br s, 1H); Mass spectrum: MH^+ 290.

Final compounds

N-(3,5-dimethoxyphenyl)-N'-(1H-indazol-4-yl)pyrimidine-2,4-diamine

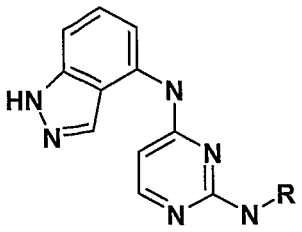


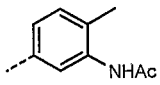
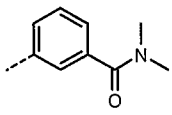
Compound 292

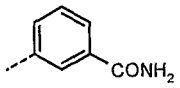
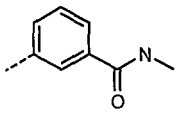
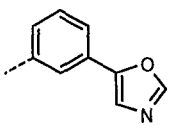
A 4N HCl solution in dioxane (0.1 ml) was added to a mixture of N-(2-methylsulfonylpyrimidin-4-yl)-1H-indazol-4-amine (87 mg, 0.3 mmol) and 3,5-dimethoxyaniline (1 eq.) in 2-pentanol (0.9 ml). The mixture was irradiated in a Personal Chemistry EMRYS™ Optimizer EXP microwave synthesisor at 170°C for 10 minutes. The reaction mixture was cooled to room temperature and purified on a preparative HPLC-MS system (Column: C18, 5 microns, 19 mm diameter, 100 mm length; elution with a gradient of water and acetonitrile containing 2g/l of ammonium carbonate); evaporation of the collected fractions gave the title compound (65 mg, 61%); NMR Spectrum : 3.66 (s, 6H), 6.09 (t, 1H), 6.47 (d, 1H), 7.04 (d, 2H), 7.20 (d, 1H), 7.28 (dd, 1H), 7.97 (d, 1H), 8.10 (s, 1H), 8.30 (s, 1H), 9.13 (s, 1H), 9.39 (s, 1H), 13.06 (s, 1H); Mass Spectrum MH^+ 363.

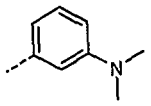
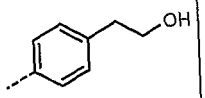
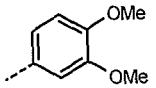
The procedure described above was repeated using the appropriate aniline. Thus were obtained the compounds described in Table 9 below.

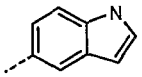
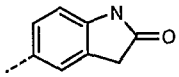
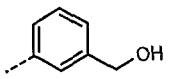
Table 9

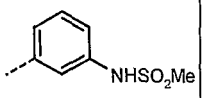


No.	Name	R	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
293	N-[5-[[4-(1H-indazol-4-ylamino)pyrimidin-2-yl]amino]-2-methyl-phenyl]acetamide		374	2.03 (s, 3H), 2.12 (s, 3H), 6.45 (d, 1H), 7.04 (d, 1H), 7.18 (d, 1H), 7.29 (dd, 1H), 7.48 (dd, 1H), 7.74 (d, 1H), 8.01 (d, 1H), 8.07 (d, 1H), 8.33 (s, 1H), 9.14 (s, 1H), 9.28 (s, 1H), 9.35 (s, 1H), 13.05 (s, 1H)
294	3-[[4-(1H-indazol-4-ylamino)pyrimidin-2-yl]amino]-N,N-dimethyl-benzamide		374	2.87 (bs, 3H), 2.97 (bs, 3H), 6.48 (d, 1H), 7.27 (d, 1H), 7.33 (dd, 1H), 7.65 (dd, 1H), 7.81 (d, 1H), 7.92 (d, 1H), 8.14 (d, 1H), 8.26 (s, 1H), 8.74 (d, 1H), 9.16 (s, 1H), 9.51 (s, 1H), 9.55 (s, 1H), 13.11 (s, 1H)

No.	Name	R	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
295	3-[[4-(1H-indazol-4-ylamino)pyrimidin-2-yl]amino]benzamide		346	6.49 (d, 1H), 7.18 (d, 1H), 7.23-7.33 (m, 3H), 7.41 (d, 1H), 7.84 (s, 1H), 7.93 (dd, 1H), 7.99 (d, 1H), 8.11 (d, 1H), 8.12 (s, 1H), 8.32 (s, 1H), 9.31 (s, 1H), 9.39 (s, 1H), 13.05 (s, 1H)
296	3-[[4-(1H-indazol-4-ylamino)pyrimidin-2-yl]amino]-N-methyl-benzamide		360	2.76 (d, 3H), 6.49 (d, 1H), 7.18 (d, 1H), 7.24 (dd, 1H), 7.29 (dd, 1H), 7.34 (ddd, 1H), 7.90 (dd, 1H), 7.98 (d, 1H), 8.10 (d, 1H), 8.12 (s, 1H), 8.29 (q, 1H), 8.32 (s, 1H), 9.33 (s, 1H), 9.39 (s, 1H), 13.05 (s, 1H)
297	N'-(1H-indazol-4-yl)-N-(3-1,3-oxazol-5-ylphenyl)pyrimidine-2,4-diamine		370	6.48 (d, 1H), 7.11-7.20 (m, 2H), 7.29 (d, 1H), 7.33 (dd, 1H), 7.50 (s, 1H), 7.74 (ddd, 1H), 7.93 (d, 1H), 8.12 (d, 1H), 8.13 (s, 1H), 8.30 (s, 1H), 8.39 (s, 1H), 9.37 (s, 1H), 9.43 (s, 1H), 13.05 (s, 1H)

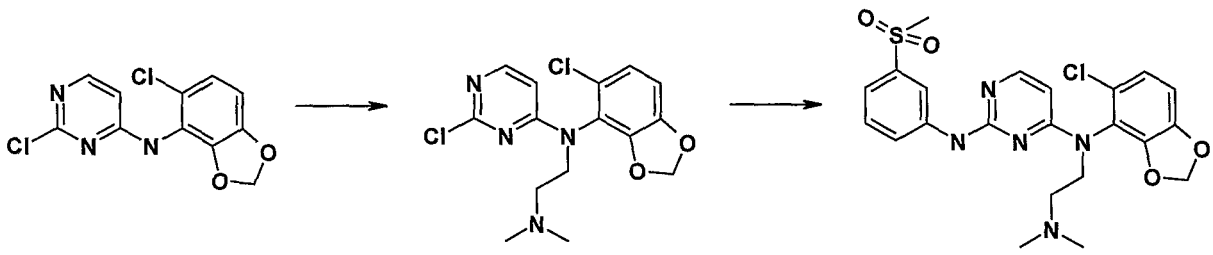
No.	Name	R	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
298	N-(3-dimethylaminophenyl)-N'-(1H-indazol-4-yl)pyrimidine-2,4-diamine		346	2.82 (s, 6H), 6.33 (dd, 1H), 6.44 (d, 1H), 7.03 (dd, 1H), 7.09 (dd, 1H), 7.16-7.21 (m, 2H), 7.26 (dd, 1H), 8.01 (d, 1H), 8.07 (d, 1H), 8.31 (s, 1H), 8.95 (s, 1H), 9.33 (s, 1H), 13.04 (s, 1H)
299	2-[4-[[4-(1H-indazol-4-ylamino)pyrimidin-2-yl]amino]phenyl]ethanol		347	2.66 (t, 2H), 3.57 (dt, 2H), 4.62 (t, 1H), 6.43 (d, 1H), 7.07 (d, 2H), 7.20 (d, 1H), 7.29 (dd, 1H), 7.62 (d, 2H), 7.95 (d, 1H), 8.07 (d, 1H), 8.30 (bs, 1H), 9.09 (s, 1H), 9.36 (s, 1H), 13.05 (s, 1H)
300	N-(3,4-dimethoxyphenyl)-N'-(1H-indazol-4-yl)pyrimidine-2,4-diamine		363	3.62 (s, 3H), 3.72 (s, 3H), 6.42 (d, 1H), 6.83 (d, 1H), 7.18 (d, 1H), 7.22-7.29 (m, 2H), 7.37 (d, 1H), 7.95 (d, 1H), 8.06 (d, 1H), 8.30 (s, 1H), 8.98 (s, 1H), 9.33 (s, 1H), 13.05 (s, 1H)

No.	Name	R	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
301	N'-(1H-indazol-4-yl)-N-(1H-indol-5-yl)pyrimidine-2,4-diamine		343	6.31 (dd, 1H), 6.39 (d, 1H), 7.17 (d, 1H), 7.21 (dd, 1H), 7.25-7.32 (m, 3H), 7.98 (s, 1H), 8.03 (d, 1H), 8.05 (d, 1H), 8.33 (s, 1H), 8.92 (s, 1H), 9.28 (s, 1H), 10.89 (s, 1H), 13.04 (s, 1H)
302	5-[[4-(1H-indazol-4-ylamino)pyrimidin-2-yl]amino]-1,3-dihydroindol-2-one		358	3.39 (s, 2H), 6.39 (d, 1H), 6.68 (d, 1H), 7.21 (d, 1H), 7.28 (dd, 1H), 7.39 (dd, 1H), 7.68 (s, 1H), 7.86 (d, 1H), 8.04 (d, 1H), 8.27 (s, 1H), 9.03 (s, 1H), 9.35 (s, 1H), 10.20 (s, 1H), 13.06 (s, 1H)
303	[3-[[4-(1H-indazol-4-ylamino)pyrimidin-2-yl]amino]phenyl]methanol		333	4.43 (d, 2H), 5.11 (t, 1H), 6.46 (d, 1H), 6.90 (d, 1H), 7.18 (dd, 1H), 7.20 (d, 1H), 7.30 (dd, 1H), 7.61 (d, 1H), 7.69 (s, 1H), 7.97 (d, 1H), 8.09 (d, 1H), 8.31 (s, 1H), 9.18 (s, 1H), 9.37 (s, 1H), 10.06 (s, 1H)

No.	Name	R	Molecular Ion ($M+H^+$)	NMR Spectrum (500 MHz, d6-DMSO)
304	N-[3-[[4-(1H-indazol-4-ylamino)pyrimidin-2-yl]amino]phenyl]methanesulfonamide		396	2.99 (s, 3H), 6.48 (d, 1H), 6.78 (ddd, 1H), 7.17 (dd, 1H), 7.19 (d, 1H), 7.31 (dd, 1H), 7.58 (s, 1H), 7.61 (d, 1H), 8.01 (d, 1H), 8.09 (d, 1H), 8.32 (s, 1H), 9.25 (s, 1H), 9.35 (s, 1H), 9.61 (bs, 1H), 13.06 (s, 1H)

Example 15

N'-(5-chlorobenzo[1,3]dioxol-4-yl)-N'-(2-dimethylaminoethyl)-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine



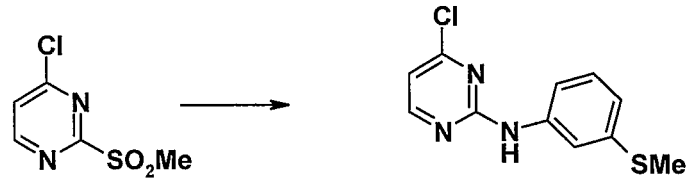
Compound 305

2-Chloro-N-(5-chloro-1,3-benzodioxol-4-yl)pyrimidin-4-amine (2.0 g, 7.07 mmol) was dissolved in DMF (20 mL). Sodium hydride (60%, 680 mg, 17 mmol) was added, followed by 2-dimethylaminoethyl chloride (hydrochloride, 1.22 g, 8.5 mmol) and the mixture was heated at 50°C overnight. After evaporation under reduced pressure, the residue was purified on silica gel chromatography (0-5% MeOH in methylene chloride) to yield N-(5-chlorobenzo[1,3]dioxol-4-yl)-N-(2-chloropyrimidin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine as a colorless oil (8.45 mg, 33%) ; NMR Spectrum (500 MHz, DMSOd6 + TFAd) 2.91 (d, 6H), 3.34 (t, 2H), 3.88-3.93 (m, 1H), 4.44-4.47 (m, 1H), 6.18-6.25 (m, 3H), 7.12 (d, 1H), 7.19 (d, 1H), 8.17 (bs, 1H); Mass Spectrum MH^+ 355.

The procedure described in Example 10 (Final compounds) was repeated using N-(5-chlorobenzo[1,3]dioxol-4-yl)-N-(2-chloropyrimidin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine (20 mg, 0.06 mmol) and 3-methylsulfonylaniline hydrochloride (13 mg, 0.06 mmol) except that the mixture was heated for 3 hours. Yield: 10 mg, 36% ; NMR Spectrum (500 MHz, DMSOd6 + TFAd) 2.69 (s, 6H), 3.27-3.29 (m, 2H), 3.29 (s, 3H), 3.91-3.95 (m, 1H), 4.45-4.50 (m, 1H), 6.02 (d, 1H), 6.23 (d, 2H), 7.16 (d, 1H), 7.23 (d, 1H), 7.73-7.82 (m, 2H), 7.91 (d, 1H), 8.10 (d, 1H), 8.21 (s, 1H) ; Mass Spectrum MH^+ 490.

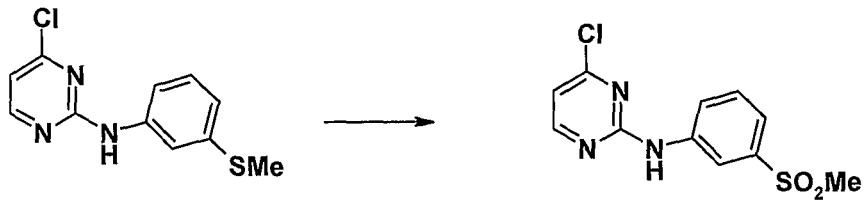
Example 16

N'-(6-chlorobenzofuran-7-yl)-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine

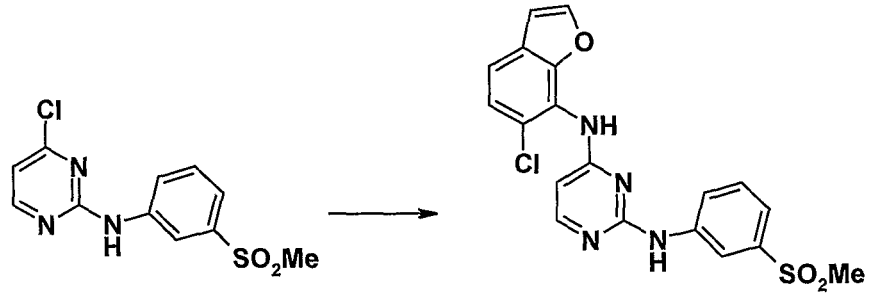


Sodium hydride (13.4 g, 60% dispersion in mineral oil) was added portion-wise to a ice-cooled solution of 3-methylthioformanilide (6.7 g, 40 mmol) [prepared by heating 3-methylthioaniline (13.9 g) in formic acid (50 ml) for 2 h at reflux, evaporation of the solvent, partitioning with ethyl acetate / aq. sodium bicarbonate and chromatography on silica gel (10% EtOAc in DCM)] in THF (200 ml). The mixture was stirred at room temperature for 10 minutes, then cooled at 0°C. 4-Chloro-2-methylsulfonylpyrimidine (8.49, 44.1 mmol, L. Xu et al, J. Org. Chem. 2003, 68, 5388) was added portionwise to the mixture. The reaction was warmed to room temperature, stirred for one hour and quenched cautiously with water. The mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated. The residue was triturated in 20 ml of diethyl ether to give N-(4-chloropyrimidin-2-yl)-N-(3-methylsulfanylphenyl)formamide as a solid (9 g). Aqueous 2N sodium hydroxide (20 ml, 40 mmol) was added to a solution of this solid (9 g) in THF – methanol (50 ml : 50 ml). After 15 minute stirring at room temperature, the mixture was evaporated under vacuum. The residue was diluted with EtOAc, washed with water and brine, dried and concentrated to give 4-chloro-N-(3-methylsulfanylphenyl)pyrimidin-2-amine (7.1 g, 71%). NMR

Spectrum (500 MHz, DMSO) 2.51 (s, 3H), 6.76 (d, 1H), 6.98 (m, 1H), 7.29 (m, 2H), 7.64 (s, 1H), 8.29 (d, 1H); Mass Spectrum MH^+ 252



m-Chloroperbenzoic acid (13.6 g, 70% strength, 55 mmol) was added portionwise to an ice-cooled solution of 4-chloro-N-(3-methylsulfanylphenyl)pyrimidin-2-amine (6.6 g, 26.3 mmol) in DCM (250 ml). The mixture was stirred at room temperature for 1 hour. The mixture was washed with aqueous sodium dithionate, aqueous sodium bicarbonate, then brine. After evaporation of the solvent, the residue was purified by chromatography on silica gel (15% EtOAc in DCM) to give 4-chloro-N-(3-methylsulfonylphenyl)pyrimidin-2-amine (6 g, 80%) as a white solid. NMR Spectrum (500 MHz, DMSO) 3.20 (s, 3H), 7.07 (d, 1H), 7.58 (m, 2H), 7.99 (m, 1H), 8.39 (s, 1H), 8.52 (d, 1H), 10.44 (s, 1H); Mass Spectrum MH^+ 284



Compound 306

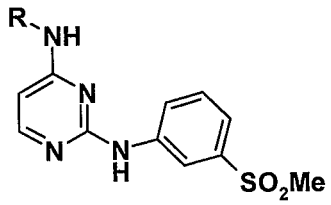
4-Chloro-N-(3-methylsulfonylphenyl)pyrimidin-2-amine (200 mg, 0.69 mmol) and 6-chlorobenzofuran-7-amine (127 mg, 0.76 mmol, Plé P. et al., J. Med. Chem. 2004, 47 , 871) were dissolved in isopropanol (3 ml). 1M HCl in diethyl ether (1 drop) added. The reaction was heated at 90°C for 1 hour then cooled to room temperature and concentrated in vacuo. The residue was directly injected on an HPLC column (C18, 5 microns, 19 mm diameter, 100 mm length) of a preparative HPLC-MS system eluting with a mixture of water and acetonitrile containing 2g/l of ammonium carbonate (gradient). After evaporation of the solvents, the mixture was repurified by chromatography on silica gel

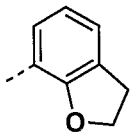
(eluting with 20% to 30% EtOAc in DCM) to give the title compound as a white solid (85 mg, 30%); NMR Spectrum (500 MHz, DMSO) 3.09 (s, 3H), 6.24 (m, 1H), 7.05 (s, 1H), 7.11 (m, 1H), 7.29 (d, 1H), 7.45 (d, 1H), 7.63 (d, 1H), 7.71 (m, 1H), 7.98 (m, 1H), 8.02 (s, 1H), 8.07 (d, 1H), 9.36 (s, 1H), 9.45 (s, 1H); Mass Spectrum MH^+ 415.

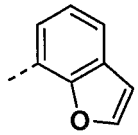
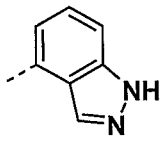
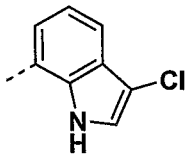
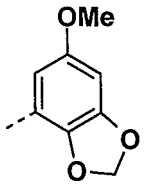
Example 17

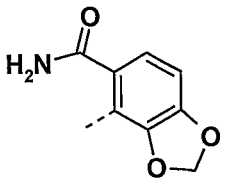
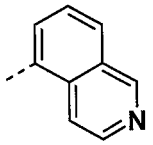
The procedure described above was repeated using the appropriate aniline. Thus were obtained the compounds described in Table 10 below

Table 10



No.	Name	R	Molecular Ion (Observed)	NMR Spectrum (500 MHz, d6-DMSO)
307 (Note 1)	N'-(2,3-dihydrobenzofuran-7-yl)-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine		383 (MH^+)	3.14 (s, 3H), 3.24 (t, 2H), 4.56 (t, 2H), 6.32 (m, 1H), 6.84 (t, 1H), 7.02 (d, 1H), 7.40 (m, 2H), 7.66 (m, 1H), 8.01 (d, 1H), 8.17 (d, 1H), 8.22 (s, 1H), 8.86 (s, 1H), 9.49 (s, 1H)

No.	Name	R	Molecular Ion (Observed)	NMR Spectrum (500 MHz, d6-DMSO)
308 (Note 2)	N'-(benzofuran-7-yl)-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine		381 (MH^+)	3.13 (s, 3H), 6.42 (m, 1H), 7.01 (d, 1H), 7.25 (m, 1H), 7.36 (m, 2H), 7.42 (m, 1H), 7.86 (m, 1H), 8.10-8.02 (m, 3H), 8.19 (s, 1H), 9.49 (s, 1H), 9.55 (s, 1H)
309	N'-(1H-indazol-4-yl)-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine		381 (MH^+)	3.16 (s, 3H), 6.53 (d, 1H), 7.21 (d, 1H), 7.32 (t, 1H), 7.43 (d, 1H), 7.48 (t, 1H), 7.94 (m, 1H), 8.15 (m, 2H), 8.29 (s, 2H), 9.46 (s, 1H), 9.61 (s, 1H)
311 (Note 3)	N'-(3-chloro-1H-indol-7-yl)-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine		414 (MH^+)	3.13 (s, 3H), 6.20 (d, 1H), 7.13 (t, 1H), 7.33 (m, 3H), 7.45 (m, 2H), 7.97 (s, 1H), 8.06 (d, 1H), 8.17 (s, 1H), 9.17 (s, 1H), 9.49 (s, 1H), 11.17 (s, 1H)
312 (Note 4)	N'-(6-methoxybenzo[1,3]dioxol-4-yl)-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine		415 (MH^+)	3.14 (s, 3H), 3.67 (s, 3H), 5.97 (s, 2H), 6.29 (d, 1H), 6.46 (d, 1H), 6.76 (s, 1H), 7.41 (m, 2H), 8.05 (d, 1H), 8.21 (m, 2H), 9.13 (s, 1H), 9.52 (s, 1H)

No.	Name	R	Molecular Ion (Observed)	NMR Spectrum (500 MHz, d6-DMSO)
313 (Note 5)	4-[[2-[(3-methylsulfonylphenyl)amino]pyrimidin-4-yl]amino]benzo[1,3]dioxole-5-carboxamide		428 (MH^+)	3.14 (s, 3H), 6.05 (s, 2H), 6.28 (d, 1H), 6.86 (d, 1H), 7.26 (d, 1H), 7.40 (m, 3H), 7.81 (s br, 1H), 8.09 (m, 2H), 8.21 (s br, 1H), 9.42 (s, 1H), 9.54 (s, 1H)
314 (Note 6)	N'-isoquinolin-5-yl-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine		392 (MH^+)	3.11 (s, 3H), 6.41 (d, 1H), 7.30 (m, 1H), 7.36 (d, 1H), 7.73 (t, 1H), 7.96 (m, 3H), 8.13 (m, 3H), 8.53 (d, 1H), 9.36 (s, 1H), 9.51 (s, 1H)

Note 1:

2,3-dihydrobenzofuran-7-amine (Birch A. et al. J. Med. Chem., 1999, 42, 3342)

Note 2:

Benzofuran-7-amine (Plé P et al., J Med. Chem, 2004, 47, 871)

Note 3:

3-Chloro-1H-indol-7-amine (Plé P et al., J Med. Chem, 2004, 47, 871)

Note 4:

6-Methoxybenzo[1,3]dioxol-4-amine (Astrazeneca, PCT Appl.WO2002016352)

Note 5:

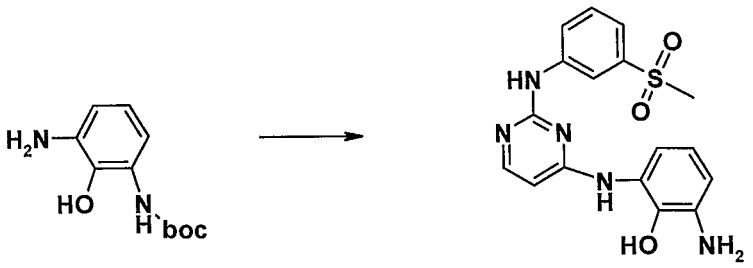
4-Aminobenzo[1,3]dioxole-5-carboxamide (Dallacker F., Annalen, 1960, 633, 14)

Note 6:

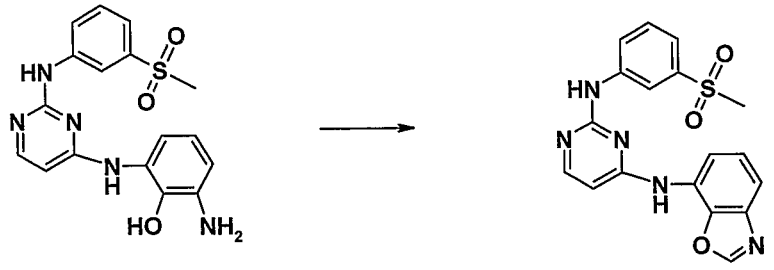
5-Aminoisoquinoline and 4-chloro-N-(3-methylsulfonylphenyl)pyrimidin-2-amine were reacted using Buchwald type conditions (procedure described in Example 24, Step 2, except that the mixture was irradiated in the microwave at 130°C for 15 minutes)

Example 18

N'-benzooxazol-7-yl-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine



The procedure described in Example 16 was repeated using tert-butyl N-(3-amino-2-hydroxy-phenyl)carbamate [365 mg, 1.6 mmol; obtained from 2,6-dinitrophenol by hydrogenation with 10% palladium over charcoal in ethanol to obtain the 2,6-diaminophenol (quantitative) and treatment of di-tert-butyldicarbonate (3.2 g, 1 eq.) in THF (50 ml) and chromatography on silica gel (eluant: 4% EtOAc in DCM)] as the aniline. After cooling, the crude mixture was concentrated and treated with 50% TFA in DCM (10 ml) for 1 hour at room temperature. After evaporation of the solvents, the residue was directly injected on an HPLC column (C18, 5 microns, 19 mm diameter, 100 mm length) of a preparative HPLC-MS system eluting with a mixture of water and acetonitrile containing 2g/l of ammonium carbonate (gradient) to give 2-amino-6-[[2-[(3-methylsulfonylphenyl)amino]pyrimidin-4-yl]amino]phenol (290 mg, 53%). NMR Spectrum: (500 MHz, DMSO) 3.13 (s, 3H), 4.7 (m, 2H), 6.25 (d, 1H), 6.49 (m, 1H), 6.61 (t, 1H), 6.71 (d, 1H), 7.42 (m, 2H), 7.97 (m, 1H), 8.16 (d, 1H), 8.26 (s, 1H), 8.71 (s, 1H), 9.53 (s, 1H); Mass spectrum: MH^+ 372.



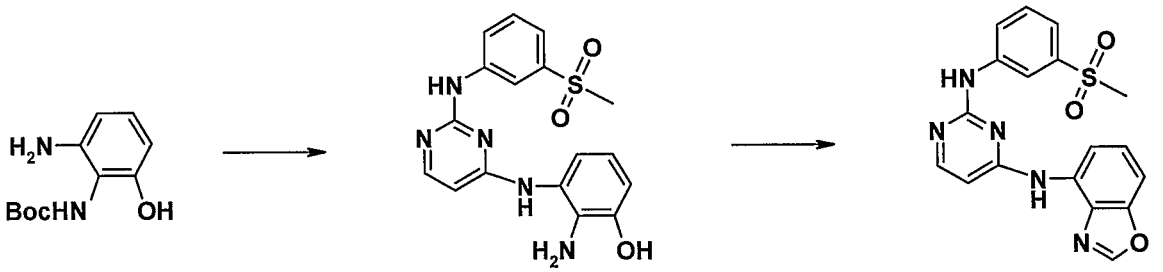
Compound 315

A mixture of 2-amino-6-[[2-[(3-methylsulfonylphenyl)amino]pyrimidin-4-yl]amino]phenol (260 mg, 0.70 mmol), trimethylorthoformate (0.614 ml, 5.6 mmol) and p-

toluenesulfonic acid (5 mg) was heated at 95°C for 30 minutes. After evaporation of the solvent, the residue was purified by chromatography on silica gel (eluant: 60% EtOAc in DCM) to give the title compound (60 mg, 22%) as white solid. NMR Spectrum: (500 MHz, DMSO) 3.14 (s, 3H), 6.45 (d, 1H), 7.41-7.33 (m, 3H), 7.55 (d, 1H), 7.91 (d, 1H), 8.00 (d, 1H), 8.13 (d, 1H), 8.19 (s, 1H), 8.75 (s, 1H), 9.57 (s, 1H), 9.69 (s, 1H); Mass spectrum: MH^+ 382.

Example 19

N'-benzooxazol-4-yl-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine



Compound 316

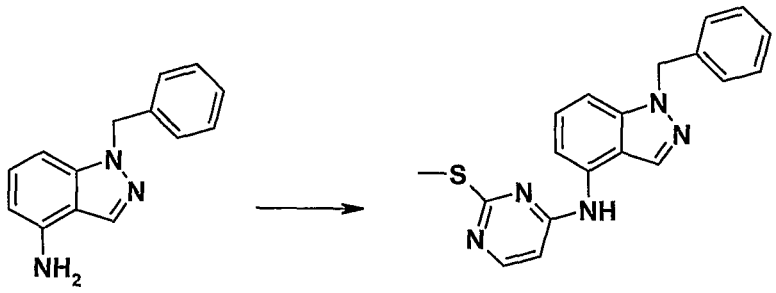
The procedure described in Example 18 was repeated using tert-butyl N-(2-amino-6-hydroxy-phenyl)carbamate (365 mg, 1.63 mmol, Astrazeneca, PCT Int. App. WO 2003053960 p 59 Ex. 3 starting material) as the aniline:

2-amino-3-[[2-[(3-methylsulfonylphenyl)amino]pyrimidin-4-yl]amino]phenol (260 mg, 47%), brown solid; NMR Spectrum: (500 MHz, DMSO) 3.14 (s, 3H), 4.30 (m, 2H), 6.05 (d, 1H), 6.48 (m, 1H), 6.62 (m, 1H), 6.73 (d, 1H), 7.39 (m, 2H), 7.96 (d, 1H), 8.20 (m, 2H), 8.51 (s, 1H), 9.30 (m, 1H), 9.43 (s, 1H); Mass spectrum: MH^+ 372.

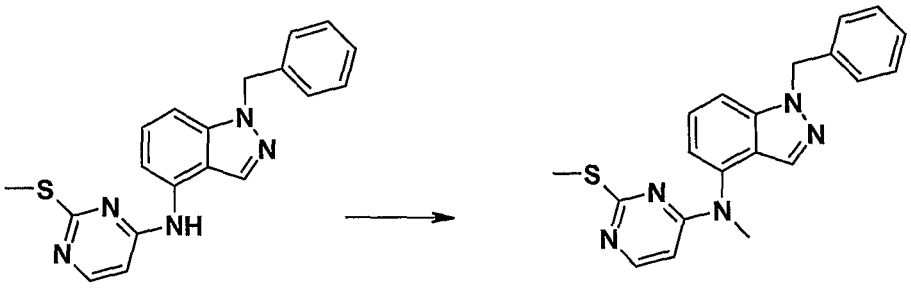
N'-benzooxazol-4-yl-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine (90 mg, 36%), white solid; NMR Spectrum: (500 MHz, DMSO) 3.16 (s, 3H), 6.68 (d, 1H), 7.50-7.39 (m, 4H), 8.14 (d, 2H), 8.32 (m, 2H), 8.76 (s, 1H), 9.63 (s, 1H), 9.67 (s, 1H); Mass spectrum: MH^+ 382.

Example 20

3-[4-(1H-indazol-4-yl-methyl-amino)pyrimidin-2-yl]-N,N-dimethyl-benzamide

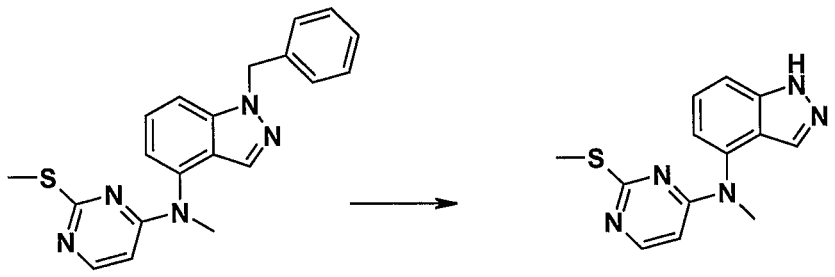


A mixture of 4-chloro-2-methylthiopyrimidine (2.4 ml, 20.7 mmol) and 1-benzylindazol-4-amine (4.15 g, 18.6 mmol, Kampe W. et al, Ger. Offen. DE2737630) and hydrogen chloride (1 drop, 4N in dioxane) in n-butanol (55 ml) was heated at reflux for 3 hours. After cooling and evaporation of the solvents, the residue was stirred with water. The pH was adjusted to 7 by addition of aqueous sodium bicarbonate and the mixture was extracted with DCM. The organic layer was washed with water and brine, and dried over $MgSO_4$. After evaporation of the solvents, the residue was purified by chromatography on silica gel (eluant: 10% to 70% EtOAc in petroleum ether) to give 1-benzyl-N-(2-methylsulfanylpyrimidin-4-yl)indazol-4-amine (5.6 g, 78%) as an orange solid. NMR Spectrum: (500 MHz, DMSO) 2.36 (s, 3H), 5.65 (s, 2H), 6.69 (d, 1H), 7.40-7.20 (m, 7H), 7.76 (d, 1H), 8.17 (d, 1H), 8.28 (s, 1H), 9.73 (s, 1H); Mass spectrum: MH^+ 348.

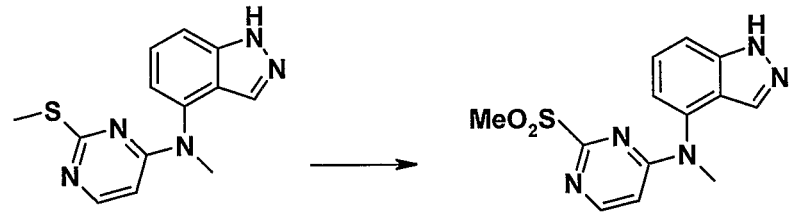


Methyl iodide (1 ml, 16.1 mmol) was added to a mixture of 1-benzyl-N-(2-methylsulfanylpyrimidin-4-yl)indazol-4-amine (5.6 g, 16.1 mmol) and cesium carbonate (10.5 g, 32.3 mmol) in acetonitrile (60 ml). The mixture was stirred at room temperature for 18 hours. The mixture was diluted with acetonitrile and the solids were filtered off. After evporation of the solvents, the residue was dissolved in DCM, filtered and purified by chromatography on silica gel (eluant: 10 to 40% EtOAc in petroleum ether) to give 1-benzyl-N-methyl-N-(2-methylsulfanylpyrimidin-4-yl)indazol-4-amine (5 g, 86%) as a

solid. NMR Spectrum: (500 MHz, DMSO) 2.41 (s, 3H), 3.52 (s, 3H), 5.70 (s, 2H), 5.95 (d, 1H), 7.13 (d, 1H), 7.34-7.25 (m, 5H), 7.47 (t, 1H), 7.75 (d, 1H), 7.91 (d, 1H), 7.96 (s, 1H).

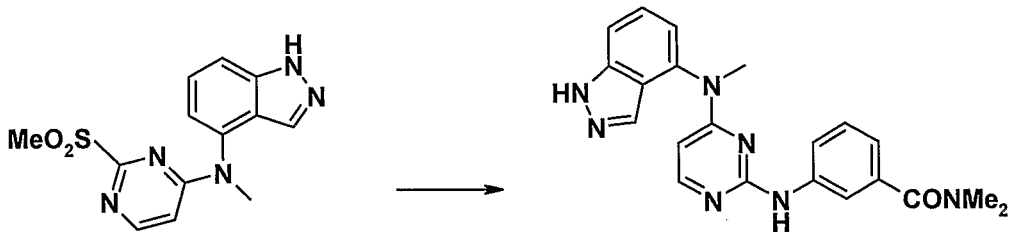


Potassium tert-butoxide (97 ml, 97 mmol, 1M solution in THF) was added to a mixture of 1-benzyl-N-methyl-N-(2-methylsulfanylpyrimidin-4-yl)indazol-4-amine (5 g, 13.85 mmol) in DMSO (9.9 ml) – THF (20 ml) at room temperature. Oxygen was bubbled through the solution for 20 minutes while maintaining the temperature below 30°C with a cooling bath. The mixture was quenched with saturated aqueous ammonium chloride and extracted with EtOAc. The organic layer was washed with water and brine, and dried over $MgSO_4$. After evaporation of the solvents, the residue was purified by chromatography on silica gel (eluant: 10% to 70% EtOAc in petroleum ether) to give N-methyl-N-(2-methylsulfanylpyrimidin-4-yl)-1H-indazol-4-amine (3.1 g, 83%) as a white solid. NMR Spectrum: (500 MHz, DMSO) 2.44 (s, 3H), 3.52 (s, 3H), 5.91 (d, 1H), 7.09 (d, 1H), 7.44 (t, 1H), 7.56 (d, 1H), 7.91 (m, 2H), 13.34 (s br, 1H).



m-Chloroperbenzoic acid (6.81 g, 27.7 mmol) was added to an ice-cooled solution of N-methyl-N-(2-methylsulfanylpyrimidin-4-yl)-1H-indazol-4-amine (3 g, 11.1 mmol) in DMF (80 ml). The mixture was then stirred at room temperature for 4 hours. The mixture was concentrated, diluted in DCM, washed with sodium bicarbonate and brine, and dried over $MgSO_4$. After evaporation of the solvents, the residue was triturated in ether and dried to give N-methyl-N-(2-methylsulfonylpyrimidin-4-yl)-1H-indazol-4-amine (2.4 g, 72%) as a

white solid. NMR Spectrum: (500 MHz, DMSO) 3.30 (s, 3H), 3.59 (s, 3H), 6.39 (m, 1H), 7.18 (d, 1H), 7.48 (t, 1H), 7.63 (d, 1H), 7.99 (s, 1H), 8.23 (d, 1H).



Compound 317

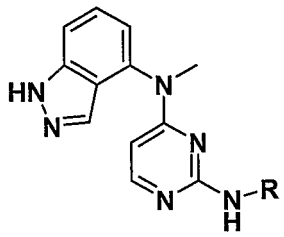
A mixture of N-methyl-N-(2-methylsulfonylpyrimidin-4-yl)-1H-indazol-4-amine (200 mg, 0.66 mmol), 3-amino-N,N-dimethyl-benzamide (130 mg, 0.79 mmol) and hydrogen chloride (4N in dioxane, 0.165 ml, 0.66 mmol) in 2-pentanol (3 ml) was irradiated in a Personal Chemistry EMRYS™ Optimizer EXP microwave synthesisor at 150°C for 15 minutes. After cooling and evaporation of the solvents, the residue was dissolved in DMF (1.5 ml) and concentrated aqueous ammonia (50 µl) was added. The mixture was injected on an HPLC column (C18, 5 microns, 19 mm diameter, 100 mm length) of a preparative HPLC-MS system eluting with a mixture of water and acetonitrile containing 2g/l of ammonium carbonate (gradient). Evaporation of the fractions gave the title compound (69 mg, 27%).

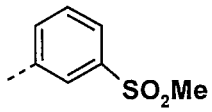
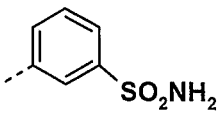
NMR Spectrum: (500 MHz, DMSO) 2.90-2.97 (br s, 3H), 2.97 (br s, 3H), 3.55 (s, 3H), 5.74 (d, 1H), 6.86 (d, 1H), 7.10 (d, 1H), 7.22 (dd, 1H), 7.45 (dd, 1H), 7.55 (d, 1H), 7.75 (d, 1H), 7.80 (d, 1H), 7.88 (d, 1H), 7.92 (s, 1H), 9.34 (s, 1H), 13.31 (br s, 1H); Mass spectrum: MH^+ 388

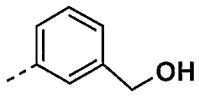
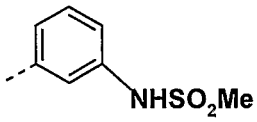
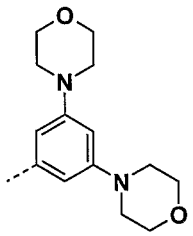
Example 21

The procedure described in Example 20 above was repeated using the appropriate aniline in the last step. Thus were obtained the compounds described in Table 11 below.

Table 11

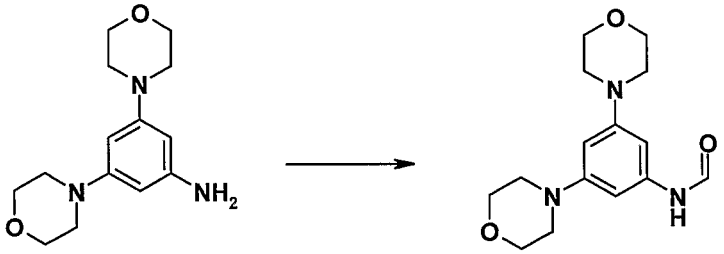


No.	Name	R	Molecular Ion (Observed)	NMR Spectrum (500 MHz, d6-DMSO)
318	N-methyl-N-[2-(3-methylsulfonylphenyl)pyrimidin-4-yl]-1H-indazol-4-amine		395 (MH^+)	3.17 (s, 3H), 3.59 (s, 3H), 5.73 (d, 1H), 7.12 (d, 1H), 7.39-7.49 (m, 3H), 7.57 (d, 1H), 7.86 (d, 1H), 7.89 (d, 1H), 7.93 (s, 1H), 8.69 (s, 1H), 9.69 (s, 1H), 13.33 (br s, 1H)
319	3-[4-(1H-indazol-4-yl-methyl-amino)pyrimidin-2-yl]benzenesulfonamide		396 (MH^+)	3.58 (s, 3H), 5.70 (d, 1H), 7.11 (d, 1H), 7.26 (br s, 2H), 7.37-7.39 (m, 2H), 7.45 (dd, 1H), 7.56 (d, 1H), 7.77 (d, 1H), 7.86 (d, 1H), 7.92 (d. 1H), 8.56 (s, 1H), 9.58 (s, 1H), 13.32 (br s, 1H)

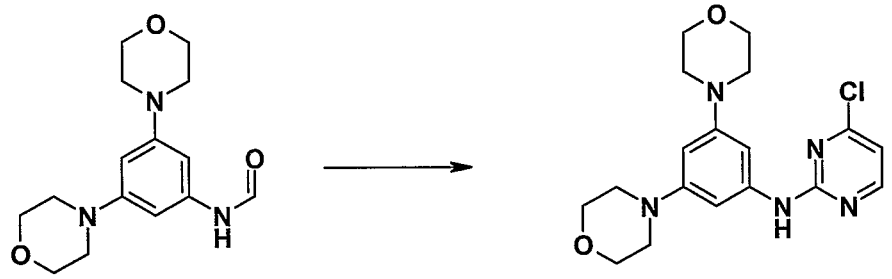
No.	Name	R	Molecular Ion (Observed)	NMR Spectrum (500 MHz, d6-DMSO)
320	[3-[4-(1H-indazol-4-yl-methyl-amino)pyrimidin-2-yl]phenyl]methanol		347 (MH^+)	3.56 (s, 3H), 4.42 (d, 2H), 5.09 (t, 1H), 5.70 (d, 1H), 6.84 (d, 1H), 7.10 (d, 1H), 7.12 (dd, 1H), 7.44 (dd, 1H), 7.52-7.58 (m, 2H), 7.76 (s, 1H), 7.85 (d, 1H), 7.91 (s, 1H), 9.17 (s, 1H), 13.31 (br s, 1H)
321	N-[3-[4-(1H-indazol-4-yl-methyl-amino)pyrimidin-2-yl]phenyl] methanesulfonamide		410 (MH^+)	2.98 (s, 3H), 3.56 (s, 3H), 5.67 (d, 1H), 6.74 (dd, 1H), 7.10 (d, 1H), 7.13 (dd, 1H), 7.44 (dd, 1H), 7.46 (d, 1H), 7.55 (d, 1H), 7.72 (s, 1H), 7.83 (d, 1H), 7.91 (s, 1H), 9.23 (s, 1H), 9.57 (bs, 1H), 13.32 (br s, 1H)
322	N-(3,5-dimorpholinophenyl)-N'-(1H-indazol-4-yl)-N'-methyl-pyrimidine-2,4-diamine		487 (MH^+)	3.04 (m, 8H), 3.56 (s, 3H), 3.71 (m, 8H), 5.62 (d, 1H), 6.11 (s, 1H), 7.01 (s, 2H), 7.09 (d, 1H), 7.43 (d, 1H), 7.54 (d, 1H), 7.81 (d, 1H), 7.93 (s, 1H), 8.88 (s, 1H), 13.31 (br s, 1H)

Example 22

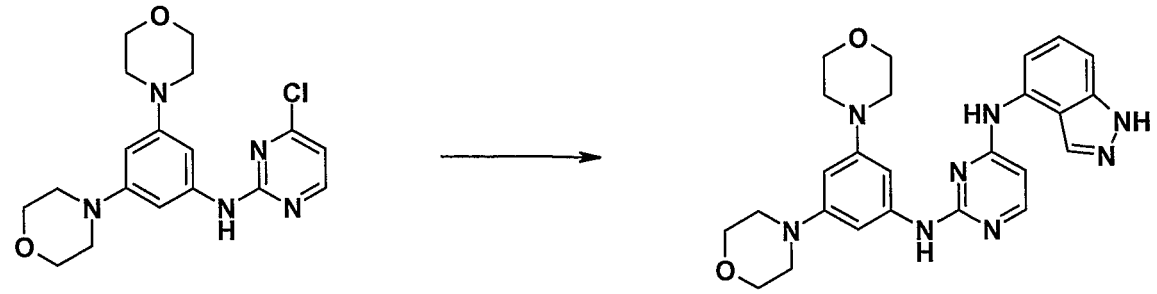
N-(3,5-dimorpholin-4-ylphenyl)-N'-(1H-indazol-4-yl)pyrimidine-2,4-diamine



A mixture of 3,5-dimorpholin-4-ylaniline (500 mg, 1.90 mmol) in formic acid (8 ml) was heated at reflux for 2 hours. After cooling, the mixture was concentrated and the residue was dissolved in EtOAc, washed with aqueous saturated sodium bicarbonate and dried over MgSO4. After evaporation of the solvents, the residue was purified by chromatography on silica gel (eluant: 1% to 4% methanol in DCM) to give 3,5-dimorpholin-4-ylformanilide (400 mg, 58%) as a solid. Mass spectrum: MH^+ 292.



3,5-Dimorpholin-4-ylformanilide (400 mg, 1.37 mmol) and 4-chloro-2-methylsulfonylpyrimidine (291 mg, 1.51 mmol) were reacted according to procedure in Example 16, step 1, to give 4-chloro-N-(3,5-dimorpholin-4-ylphenyl)pyrimidin-2-amine (314 mg, 61%) as a solid. NMR Spectrum: (500 MHz, DMSO) 3.06 (m, 8H), 3.72 (m, 8H), 6.19 (s, 1H), 6.91 (m, 3H), 8.41 (d, 1H), 9.74 (s, 1H); Mass spectrum: MH^+ 376.



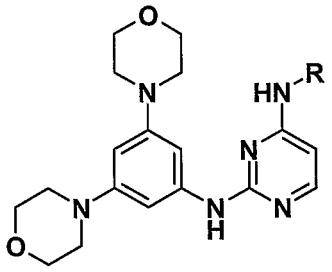
Compound 323

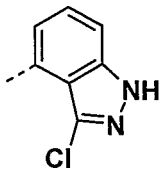
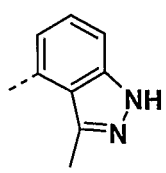
4-chloro-N-(3,5-dimorpholin-4-ylphenyl)pyrimidin-2-amine (100 mg, 0.27 mmol) and 4-aminoindazole (39 mg, 0.29 mmol) were reacted according to the procedure in Example 16, step 3, to give the title compound (70 mg, 56%) as a solid. NMR Spectrum: (500 MHz, DMSO) 2.96 (m, 8H), 3.66 (m, 8H), 6.09 (s, 1H), 6.42 (d, 1H), 6.88 (s, 2H), 7.18 (d, 1H), 7.25 (t, 1H), 7.91 (m, 1H), 8.07 (d, 1H), 8.27 (s, 1H), 8.87 (s, 1H), 9.33 (s, 1H), 13.03 (m, 1H); Mass spectrum: MH^+ 473.

Example 23

The procedure described above in Example 22, step 3 was repeated using the appropriate aniline. Thus were obtained the compounds described in Table 12 below.

Table 12



No.	Name	R	Molecular Ion (Observed)	NMR Spectrum (500 MHz, d6-DMSO)
325 (Note 1)	N'-(3-chloro-1H-indazol-4-yl)-N-(3,5-dimorpholinophenyl) pyrimidine-2,4-diamine		507 (MH^+)	2.90 (m, 8H), 3.65 (m, 8H), 6.02 (s, 1H), 6.18 (d, 1H), 6.83 (s, 2H), 7.39-7.28 (m, 3H), 8.01 (d, 1H), 8.74 (s, 1H), 8.91 (s, 1H), 13.3 (m, 1H)
326 (Note 2)	N-(3,5-dimorpholinophenyl) -N'-(3-methyl-1H-indazol-4-yl)pyrimidine-2,4-diamine		487 (MH^+)	2.47 (s, 3H), 2.90 (m, 8H), 3.65 (m, 8H), 6.02 (s, 1H), 6.06 (d, 1H), 6.86 (s, 2H), 7.07 (m, 1H), 7.28 (m, 2H), 7.97 (d, 1H), 8.71 (s, 1H),

No.	Name	R	Molecular Ion (Observed)	NMR Spectrum (500 MHz, d6-DMSO)
				8.91 (s, 1H), 12.66 (m, 1H)

Note 1: 3-chloro-1H-indazol-4-amine was made as follows:

3-Chloro-4-nitro-1H-indazole (500 mg, 2.54 mmol; M. Benchidmi et al., J. Het. Chem., 1979, 16, 1599) in ethanol (20 ml) was hydrogenated at atmospheric pressure in the presence of platinum(IV) oxide (50 mg) at room temperature for 1 hour. After filtration of the catalyst, the mixture was concentrated and purified by chromatography on silica gel (eluant: 0% to 6% EtOAc in DCM) to give 3-chloro-1H-indazol-4-amine (242 mg, 57%) as an orange solid. NMR Spectrum: (500 MHz, DMSO) 5.57 (s, 2H), 6.21 (d, 1H), 6.61 (d, 1H), 7.05 (t, 1H), 12.84 (m, 1H); Mass spectrum: MH^+ 168.

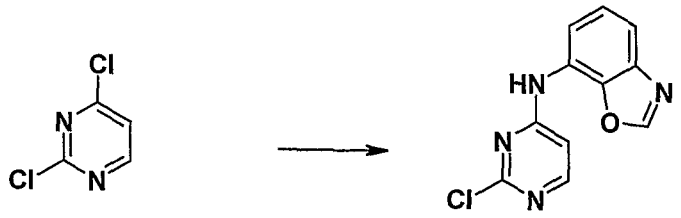
Note 2: 3-methyl-1H-indazol-4-amine was made as follows:

A solution of dimethylzinc (2.07 ml, 4.14 mmol, 2M in toluene was added dropwise to a mixture of 3-bromo-4-nitro-1H-indazole (500 mg, 2.07 mmol; M. Benchidmi et al., J. Het. Chem., 1979, 16, 1599) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (43 mg, 0.062 mmol) in 1,4-dioxane (8 ml) under argon. The mixture was heated under reflux for 2 hours. After cooling, methanol (0.5 ml) was added, followed by 2N hydrochloric acid (3 ml) and DCM (10 ml). This mixture was stirred for 30 minutes. The organic layer was collected, washed with saturated aqueous sodium bicarbonate, water and brine, and dried over MgSO4. This solution was concentrated under vacuum to give 3-methyl-4-nitro-1H-indazole (235 mg, 64%) as a solid used without purification in the next step. NMR Spectrum: (500 MHz, DMSO) 2.61 (s, 3H), 7.52 (m, 1H), 7.93 (m, 2H), 13.54 (m, 1H); Mass spectrum: MH^+ 178.

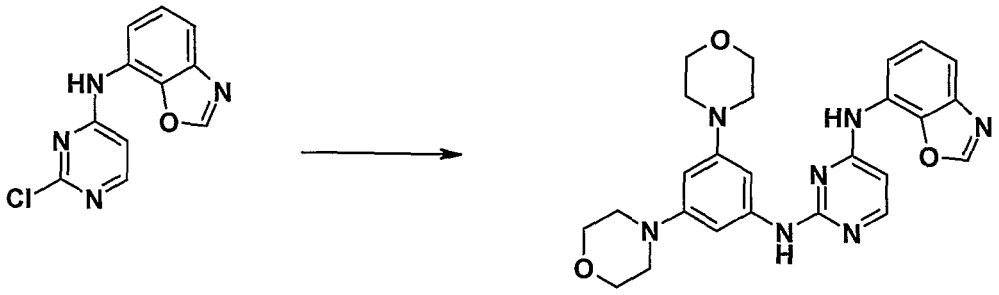
3-Methyl-4-nitro-1H-indazole (100 mg, 0.56 mmol) in ethanol (10 ml) was hydrogenated at atmospheric pressure in the presence of platinum(IV) oxide (10 mg) at room temperature for 1 hour. After filtration of the catalyst, the mixture was concentrated to give 3-methyl-1H-indazol-4-amine (90 mg, 75%) as a yellow solid. NMR Spectrum: (500 MHz, DMSO) 2.58 (s, 3H), 5.26 (s, 2H), 6.12 (d, 1H), 6.55 (d, 1H), 6.92 (t, 1H), 12.14 (m, 1H); Mass spectrum: MH^+ 148.

Example 24

N'-benzooxazol-7-yl-N-(3,5-dimorpholin-4-ylphenyl)pyrimidine-2,4-diamine



A mixture of benzooxazol-7-amine (135 mg, 1.01 mmol, Astrazeneca, PCT Appl. WO2003053960), 2.4-dichloropyrimidine (150 mg, 1.01 mmol), DBU (0.197 ml, 1.32 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (58 mg, 0.1 mmol, also named xantphos) and tris(dibenzylideneacetone)dipalladium(0) (58 mg, 0.1 mmol, also named Pd2dba3) in dioxane (3 ml) under argon was irradiated in a Personal Chemistry EMRYS™ Optimizer EXP microwave synthesisor at 110°C for 10 minutes. After cooling and evaporation of the solvents, the residue was dissolved in DCM and purified by chromatography on silica gel (eluant: 30% to 60% EtOAc in petroleum ether) to give N-(2-chloropyrimidin-4-yl)benzooxazol-7-amine (88 mg, 35%) as a beige solid. Mass spectrum: MH^+ 247



Compound 327

A mixture of N-(2-chloropyrimidin-4-yl)benzooxazol-7-amine (75 mg, 0.3 mmol), 3,5-dimorpholin-4-ylaniline (79 mg, 0.3 mmol), DBU (60 µl, 0.4 mmol), xantphos (17 mg, 0.03 mmol) and Pd2dba3 (17 mg, 0.03 mmol) in dioxane (2 ml) under argon was irradiated in a Personal Chemistry EMRYS™ Optimizer EXP microwave synthesisor at 150°C for 20 minutes. After cooling, concentrated aqueous ammonia (2 drops) was added and the mixture was injected on an HPLC column (C18, 5 microns, 19 mm diameter, 100 mm length) of a preparative HPLC-MS system eluting with a mixture of water and acetonitrile containing 2g/l of ammonium carbonate (gradient). Evaporation of the

fractions gave the title compound (20 mg, 14%). NMR Spectrum: (500 MHz, DMSO) 2.92 (m, 8H), 3.65 (m, 8H), 6.06 (s, 1H), 6.352 (d, 1H), 6.82 (s, 2H), 7.33 (t, 1H), 7.50 (d, 1H), 7.98 (d br, 1H), 8.06 (d, 1H), 8.74 (s, 1H), 8.85 (s, 1H), 9.55 (s, 1H); Mass spectrum: MH^+ 474.

Example 25

N'-benzooxazol-7-yl-N-(3,5-dimorpholinophenyl)-N'-methyl-pyrimidine-2,4-diamine (compound 328)

N-(2-chloropyrimidin-4-yl)benzooxazol-7-amine (600 mg, 2.44 mmol) was reacted with methyl iodide according to the procedure of Example 10 (starting material (1)) to give N-(2-chloropyrimidin-4-yl)-N-methyl-benzooxazol-7-amine (363 mg, 57%) as a gum. NMR Spectrum: (500 MHz, DMSO) 3.50 (s, 3H), 6.43 (m, 1H), 7.53 (m, 2H), 7.84 (m, 1H), 8.10 (m, 1H), 8.79 (s, 1H).

N-(2-chloropyrimidin-4-yl)-N-methyl-benzooxazol-7-amine (180 mg, 0.69 mmol) was reacted with 3,5-dimorpholin-4-ylaniline according to the procedure in Example 24, Step 2 to give the title compound (15 mg, 4%) as a white solid; NMR Spectrum (500 MHz, DMSO) 2.99-3.05 (m, 8H), 3.53 (s, 3H), 3.67-3.73 (m, 8H), 5.75 (d, 1H), 6.10 (t, 1H), 6.93 (d, 2H), 7.45 (d, 1H), 7.48 (d, 1H), 7.50 (s, 1H), 7.78 (dd, 1H), 7.92 (d, 1H), 8.90 (bs, 1H); Mass spectrum: MH^+ 488.

Example 26

N-(3,5-dimorpholin-4-ylphenyl)-N'-methyl-N'-(3-methyl-1H-indazol-4-yl)pyrimidine-2,4-diamine (compound 329)

Iodine (9.31 g, 36.8 mmol) and potassium hydroxide (3.81 g, 68.1 mmol) were added to a solution of 4-nitro-1H-indazole (3 g, 18.4 mmol) in DMF (40 ml) at room temperature. The mixture was stirred at room temperature for 2.5 hours., and poured in 10% aqueous sodium hydrogensulfite (200 ml). The precipitate was filtered, washed with water and dried over phosphorus pentoxide to give 3-iodo-4-nitro-1H-indazole (5 g, 94%) as a light yellow solid.

NMR Spectrum: (500 MHz, DMSO) 7.60 (t, 1H), 7.86 (d, 1H), 8.00 (d, 1H), 14.3 (m, 1H); Mass spectrum: $M\text{-}H^-$ 288

Potassium tert-butoxide (23.5 ml, 1M in THF, 23.5 mmol) was added dropwise to an ice-cooled solution of 3-iodo-4-nitro-1H-indazole (4.85 g, 16.8 mmol) in THF (30 ml) under argon. The mixture was stirred at 0°C for 1 hour. 4-Methoxybenzyl chloride (2.5 ml, 18.5 mmol) and tetrabutylammonium iodide (63 mg, 0.17 mmol) were added and the mixture was stirred at 70°C for 2.5 hours. The mixture was cooled and concentrated under vacuum. The residue was dissolved in ethyl acetate, washed with water and brine and dried over MgSO4. After evaporation of the solvents, the residue was purified by chromatography on silica gel (eluant: 10% to 40% EtOAc in petroleum ether) to give 3-iodo-1-[(4-methoxyphenyl)methyl]-4-nitro-indazole (4.4 g, 64%) as a solid. NMR Spectrum: (500 MHz, DMSO) 3.71 (s, 3H), 5.71 (s, 2H), 6.89 (d, 2H), 7.25 (d, 2H), 7.64 (t, 1H), 7.87 (d, 1H), 8.27 (d, 1H).

A solution of dimethylzinc (9.05 ml, 18.1 mmol, 2M in toluene) was added dropwise to a mixture of 3-iodo-1-[(4-methoxyphenyl)methyl]-4-nitro-indazole (3.7 g, 9.05 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (189 mg, 0.27 mmol) in 1,4-dioxane (30 ml) under argon. The mixture was heated at 100°C for 1.5 hour. After cooling, methanol (3 ml) was added, followed by 2N hydrochloric acid until the pH was acidic. This mixture was stirred for 10 minutes, extracted with EtOAc, washed with saturated aqueous sodium bicarbonate, water and brine, and dried over MgSO4. After evaporation of the solvents, the residue was purified by chromatography on silica gel (eluant: 10% to 25% EtOAc in petroleum ether) to give 1-[(4-methoxyphenyl)methyl]-3-methyl-4-nitro-indazole (1.07 g, 40%) as a yellow solid. NMR Spectrum: (500 MHz, DMSO) 2.59 (s, 3H), 3.70 (s, 3H), 5.61 (s, 2H), 6.87 (d, 2H), 7.22 (d, 2H), 7.56 (t, 1H), 7.92 (d, 1H), 8.19 (d, 1H).

1-[(4-Methoxyphenyl)methyl]-3-methyl-4-nitro-indazole (1 g, 3.37 mmol) in ethanol (30 ml) was hydrogenated at atmospheric pressure in the presence of platinum(IV) oxide (80 mg) at room temperature for 1 hour. After filtration of the catalyst, the mixture was concentrated to give 1-[(4-methoxyphenyl)methyl]-3-methylindazol-4-amine (900 mg, 100%) as a yellow gum. NMR Spectrum: (500 MHz, DMSO) 2.58 (s, 3H), 3.68 (s, 3H), 5.30 (s, 2H), 5.33 (s, 2H), 6.15 (d, 1H), 6.66 (d, 1H), 6.84 (d, 2H), 6.95 (t, 1H), 7.13 (d, 2H); Mass spectrum: MH^+ 268.

A mixture of 4-chloro-2-methylthiopyrimidine (0.4 ml, 3.45 mmol), 1-[(4-methoxyphenyl)methyl]-3-methylindazol-4-amine (0.83 g, 3.11 mmol) and hydrogen

chloride (1 drop, 7N in dioxane) in n-butanol (10 ml) was heated at 80°C for 2 hours. After cooling and evaporation of the solvents, water was added. The pH was adjusted to 8 by addition of aqueous ammonia and the mixture was extracted with EtOAc. The precipitate which had formed at the interface was filtered, washed with water and ether and dried to give a solid. The organic layer was washed with water and brine, and dried over $MgSO_4$. After evaporation of the solvents, the residue was triturated with ether. The two batches were combined to give 1-[(4-methoxyphenyl)methyl]-3-methyl-N-(2-methylsulfanylpyrimidin-4-yl)indazol-4-amine (1 g, 74%) as a white solid. NMR Spectrum: (500 MHz, DMSO) 2.31 (s, 3H), 2.41 (s, 3H), 3.70 (s, 3H), 5.47 (s, 2H), 6.28 (d, 1H), 6.86 (d, 2H), 7.02 (d, 1H), 7.19 (d, 2H), 7.33 (t, 1H), 7.50 (d, 1H), 8.05 (d, 1H), 9.41 (s, 1H); Mass spectrum: MH^+ 392.

Methyl iodide (0.17 ml, 2.69 mmol) was added to a mixture of 1-[(4-methoxyphenyl)methyl]-3-methyl-N-(2-methylsulfanylpyrimidin-4-yl)indazol-4-amine (1 g, 2.56 mmol) and cesium carbonate (1.25 g, 3.84 mmol) in acetonitrile (6 ml). The mixture was stirred at room temperature for 18 hours. The mixture was diluted with acetonitrile and the solids were filtered off. After evaporation of the solvents, the residue was dissolved in DCM, filtered and purified by chromatography on silica gel (eluant: 10 to 40% EtOAc in petroleum ether) to give 1-[(4-methoxyphenyl)methyl]-N,3-dimethyl-N-(2-methylsulfanylpyrimidin-4-yl)indazol-4-amine (0.7 g, 67%) as a solid. Mass spectrum: MH^+ 406.

m-Chloroperbenzoic acid (909 mg, 3.7 mmol) was added to an ice-cooled solution of 1-[(4-methoxyphenyl)methyl]-N,3-dimethyl-N-(2-methylsulfanylpyrimidin-4-yl)indazol-4-amine (600 mg, 1.48 mmol) in DMF (17 ml). The mixture was then stirred at room temperature for 1.5 hour. 10% Aqueous sodium metabisulfite was added. The mixture was concentrated, diluted in DCM, washed with sodium bicarbonate and brine, and dried over $MgSO_4$. After evaporation of the solvents, the residue was purified by chromatography on silica gel (eluant: 10 to 50% EtOAc in petroleum ether) to give 1-[(4-methoxyphenyl)methyl]-N,3-dimethyl-N-(2-methylsulfonylpyrimidin-4-yl)indazol-4-amine (0.6 g, 92%) as a solid. NMR Spectrum: (500 MHz, DMSO) 2.17 (s, 3H), 3.39 (s, 3H), 3.51 (s, 3H), 3.71 (s, 3H), 5.53 (m, 2H), 6.04 (d, 1H), 6.89 (d, 2H), 7.12 (d, 1H), 7.28 (d, 2H), 7.50 (t, 1H), 7.82 (d, 1H), 8.15 (d, 1H).

A mixture of 1-[(4-methoxyphenyl)methyl]-N,3-dimethyl-N-(2-methylsulfonylpyrimidin-4-yl)indazol-4-amine (200 mg, 0.46 mmol), 3,5-dimorpholin-4-ylaniline (127 mg, 0.46 mmol) and hydrogen chloride (4N in dioxane, 7 drops) in 2-pentanol (4 ml) was irradiated in a Personal Chemistry EMRYS™ Optimizer EXP microwave synthesisor at 150°C for 30 minutes. After cooling and evaporation of the solvents, water was added. The pH was adjusted to pH 7 by addition of aqueous ammonia. The mixture was extracted with EtOAc. The organic layer was washed with sodium bicarbonate and brine, and dried over $MgSO_4$. After evaporation of the solvents, the residue was purified by chromatography on silica gel (eluant: 0 to 5% methanol in EtOAc-DCM (1:4)) to give N-(3,5-dimorpholin-4-ylphenyl)-N'-[1-[(4-methoxyphenyl)methyl]-3-methyl-indazol-4-yl]-N'-methyl-pyrimidine-2,4-diamine (71 mg, 25%); Mass spectrum: MH^+ 621.

A mixture of N-(3,5-dimorpholin-4-ylphenyl)-N'-[1-[(4-methoxyphenyl)methyl]-3-methyl-indazol-4-yl]-N'-methyl-pyrimidine-2,4-diamine (100 mg, 0.16 mmol) and anisole (1 drop) in TFA (1 ml) was irradiated in a Personal Chemistry EMRYS™ Optimizer EXP microwave synthesisor at 130°C for 40 minutes. After cooling and evaporation of the solvents, the residue was dissolved in DCM. A few drops of 6N ammonia in methanol followed by water (0.5 ml) was added. The organic layer was collected and purified by chromatography on silica gel (eluant: 0 to 5% methanol in DCM). Trituration of the resulting solid in ether gave the title compound (54 mg, 67%) as a white solid. NMR Spectrum: (500 MHz, DMSO) 2.20 (s, 3H), 3.07 (m, 8H), 3.56 (s, 3H), 3.72 (m, 8H), 5.23 (br s, 1H), 6.12 (br s, 1H), 7.02 (m, 3H), 7.41 (m, 1H), 7.51 (m, 1H), 7.75 (br s, 1H), 8.89 (br s, 1H), 12.9 (m, 1H); Mass spectrum: MH^+ 501.

Example 27

N'-methyl-N'-(3-methyl-1H-indazol-4-yl)-N-(3-methylsulfonylphenyl)pyrimidine-2,4-diamine(compound 330)

The last 2 steps from procedure in Example 26 were repeated using 1-[(4-methoxyphenyl)methyl]-N,3-dimethyl-N-(2-methylsulfonylpyrimidin-4-yl)indazol-4-amine (286 mg, 0.65 mmol) and 3-methylsulfonylaniline hydrochloride (142 mg, 0.65 mmol) to give the title compound (61 mg, 23% over 2 steps). NMR Spectrum: (500 MHz, DMSO) 2.20 (s, 3H), 3.17 (s, 3H), 3.53 (s, 3H), 5.34 (br s, 1H), 7.03 (br d, 1H), 7.43 (m,

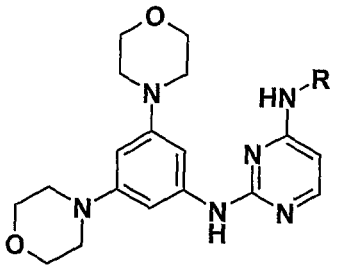
2H), 7.54 (m, 2H), 7.91-7.82 (m, 2H), 8.82 (br s, 1H), 9.70 (br s, 1H), 12.9 (m, 1H); Mass spectrum: MH^+ 409.

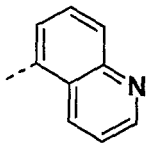
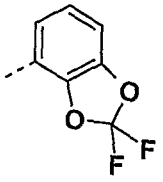
Example 28

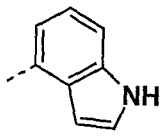
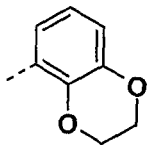
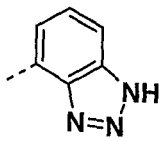
4-Chloro-N-(3,5-dimorpholin-4-ylphenyl)pyrimidin-2-amine (70 mg, 0.19 mmol) and the corresponding aniline (0.22 mmol) were dissolved in pentanol (1 ml). 4M HCl in dioxane (0.1 ml) was added. The reaction was heated at 100°C for 15 hours then cooled to room temperature and concentrated in vacuo. The residue was dissolved in DMF (1 ml) and directly injected on an HPLC column (C18, 5 microns, 19 mm diameter, 100 mm length) of a preparative HPLC-MS system eluting with a mixture of water and acetonitrile containing 2g/l of ammonium carbonate (gradient). Evaporation of the solvents gave the title compound as a solid.

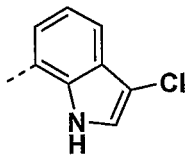
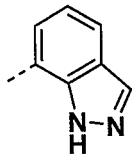
The examples in the Table 13 below were made according to the procedure above.

Table 13



No.	Name	R	Molecular Ion (Observed)	NMR Spectrum (500 MHz, d6-DMSO)
331	N-(3,5-dimorpholin-4-ylphenyl)-N'-quinolin-5-yl-pyrimidine-2,4-diamine		484 (MH^+)	2.79-2.96 (m, 8H), 3.55-3.69 (m, 8H), 6.03 (s, 1H), 6.28 (d, 2H), 6.82 (s, 1H), 7.57 (dd, 1H), 7.74 (dd, 1H), 7.85 (d, 1H), 7.93 (d, 1H), 8.05 (d, 1H), 8.52 (d, 1H), 8.78 (s, 1H), 8.93 (dd, 1H), 9.36 (s, 1H)
332	N'-(2,2-difluorobenzo[1,3]dioxol-4-yl)-N-(3,5-dimorpholin-4-ylphenyl)pyrimidine-2,4-diamine		513 (MH^+)	2.88-3.02 (m, 8H), 3.62-3.76 (m, 8H), 6.09 (s, 1H), 6.33 (d, 1H), 6.82 (s, 2H), 7.09-7.17 (m, 2H), 7.82 (d, 1H), 8.08 (d, 1H), 8.90 (s, 1H), 9.45 (s, 1H)

No.	Name	R	Molecular Ion (Observed)	NMR Spectrum (500 MHz, d6-DMSO)
333	N-(3,5-dimorpholin-4-ylphenyl)-N'-(1H-indol-4-yl)pyrimidine-2,4-diamine		472 (MH^+)	2.87-3.06 (m, 8H), 3.59-3.75 (m, 8H), 6.07 (s, 1H), 6.32 (d, 1H), 6.63 (t, 1H), 6.91 (d, 2H), 7.03 (dd, 1H), 7.15 (d, 1H), 7.29 (dd, 1H), 7.66 (d, 1H), 7.99 (d, 1H), 8.75 (s, 1H), 8.94 (s, 1H), 11.12 (s, 1H)
334	N-(3,5-dimorpholin-4-ylphenyl)-N'-(2,5-dioxabicyclo[4.4.0]deca-6,8,10-trien-10-yl)pyrimidine-2,4-diamine		491 (MH^+)	2.90-3.06 (m, 8H), 3.62-3.76 (m, 8H), 4.23-4.33 (m, 4H), 6.08 (t, 1H), 6.32 (d, 1H), 6.61 (dd, 1H), 6.76 (dd, 1H), 6.88 (d, 2H), 7.58 (d, 1H), 7.97 (d, 1H), 8.52 (s, 1H), 8.76 (s, 1H)
335	N'-(1H-benzotriazol-4-yl)-N-(3,5-dimorpholin-4-ylphenyl)pyrimidine-2,4-diamine		474 (MH^+)	2.88-3.09 (m, 8H), 3.71-3.76 (m, 8H), 6.11 (s, 1H), 6.60 (bs, 1H), 6.87 (s, 2H), 7.38 (dd, 1H), 7.44 (bs, 1H), 8.10 (d, 1H), 8.25 (bs, 1H), 8.93 (s, 1H), 9.81 (bs, 1H)

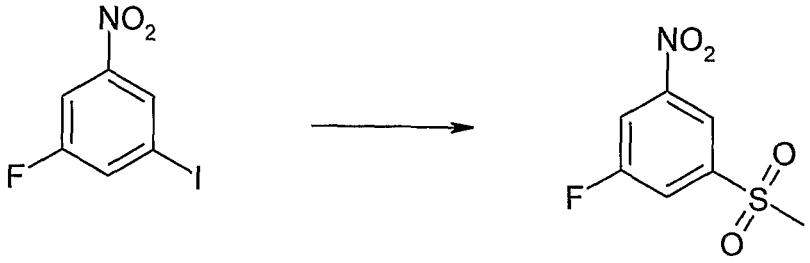
No.	Name	R	Molecular Ion (Observed)	NMR Spectrum (500 MHz, d6-DMSO)
336 (Note 1)	N'-(3-chloro-1H-indol-7-yl)-N-(3,5-dimorpholin-4-ylphenyl)pyrimidine-2,4-diamine		506 (MH^+)	2.82-3.04 (m, 8H), 3.56-3.78 (m, 8H), 6.06 (d, 1H), 6.12 (d, 1H), 6.85 (s, 2H), 7.10 (dd, 1H), 7.29 (d, 1H), 7.48 (d, 1H), 7.55 (d, 1H), 8.01 (d, 1H), 8.78 (s, 1H), 8.98 (s, 1H), 11.11 (s, 1H)
337	N-(3,5-dimorpholin-4-ylphenyl)-N'-(1H-indazol-7-yl)pyrimidine-2,4-diamine		473 (MH^+)	2.84-3.02 (m, 8H), 3.57-3.76 (m, 8H), 6.06 (s, 1H), 6.16 (d, 1H), 6.85 (s, 2H), 7.09 (dd, 1H), 7.53 (d, 1H), 7.75 (d, 1H), 8.04 (d, 1H), 8.09 (s, 1H), 8.82 (s, 1H), 9.09 (s, 1H), 12.81 (s, 1H)

Note 1: 3-chloro-1H-indol-7-amine (AstraZeneca, PCT Appl.WO200234744)

Method Section

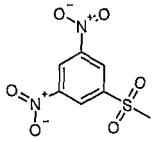
Method 1

1-Fluoro-3-methylsulfonyl-5-nitro-benzene



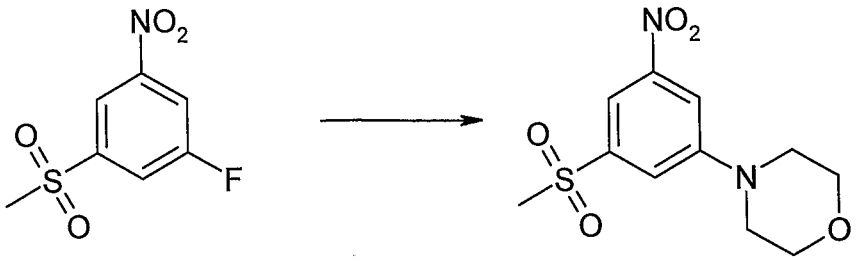
A mixture of 1-fluoro-3-iodo-5-nitro-benzene (1.95 g), copper (I) iodide (2.23 g) and sodium methansulfinate (0.75 g, 85%) in DMF (25 ml) was heated at 110°C overnight, then poured into a mixture of ethyl acetate and water and filtered. The organic layer was separated, dried and concentrated in vacuo and the residue triturated with methanol to give the title compound as a brown solid (0.6 g, 37%); NMR Spectrum (300 MHz, DMSO) 3.40 (s, 3H), 8.31 (m, 1H), 8.52 (m, 2H); Mass Spectrum M^+ 219.0.

The procedure described above was repeated using the appropriate iodobenzene. Thus was obtained the example described below:

Method	Name	Structure	Molecular Ion (Observed)	NMR Spectrum (300 MHz, d6-DMSO)
1a	1-methylsulfonyl-3,5-dinitro-benzene		247.39 (MH+)	3.50 (s, 3H), 9.00 (m, 2H), 9.09 (m, 1H)

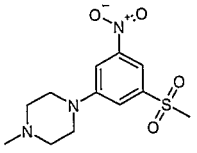
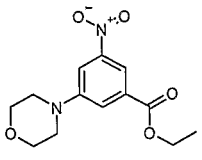
Method 2

4-(3-Methylsulfonyl-5-nitro-phenyl)morpholine



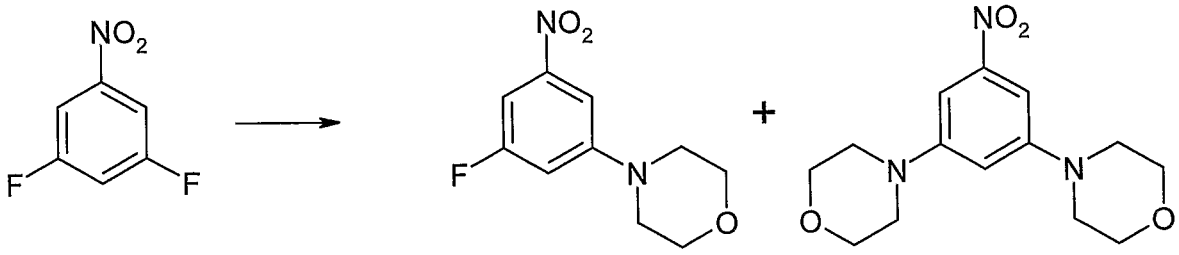
Morpholine (0.77 ml) and 1-fluoro-3-methylsulfonyl-5-nitro-benzene (0.35 g – Method 1) in DMSO (15 ml) were heated at 100°C for 6 hrs. The solution was cooled, poured into water and the resulting precipitate filtered and dried to give the title compound as an orange solid (0.39 g, 85%); NMR Spectrum (300 MHz, DMSO) 3.25 - 3.42 (m + s, 7H), 3.76 (m, 4H), 7.75 (m, 1H), 7.94 (m, 2H).

The procedure described above was repeated using the appropriate fluorobenzene. Thus were obtained the examples described below:

Method	Name	Structure	Molecular Ion (Observed)	NMR Spectrum (300 MHz, d6-DMSO)
2a	1-methyl-4-(3-methylsulfonyl-5-nitro-phenyl) piperazine		300.44 (MH+)	
2b	ethyl 3-morpholin-4-yl-5-nitro-benzoate		281.47 (MH+)	1.35 (t, 3H), 3.30 (m, 4H), 3.77 (m, 4H), 4.37 (q, 2H), 7.80 (m, 1H), 7.90 (m, 1H), 8.00 (s, 1H)

Method 3

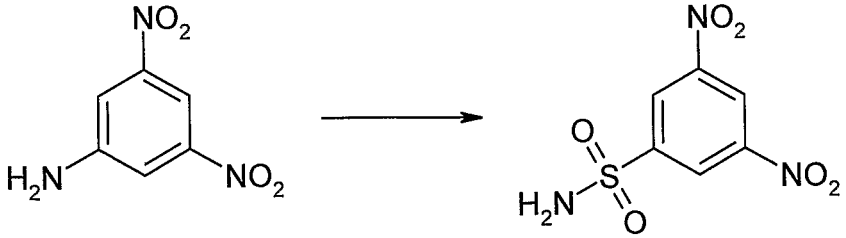
4-(3-Fluoro-5-nitro-phenyl)morpholine and 4-(3-morpholin-4-yl-5-nitro-phenyl)morpholine



Morpholine (12 ml) and 1,3-difluoro-5-nitro-benzene (4 g) in DMSO (50 ml) were heated at 100°C for 4 days. The solution was cooled, poured into water and the resulting precipitate filtered and dried. This was purified by chromatography using 25% to 60% ethyl acetate in iso-hexane as eluent to give firstly 4-(3-fluoro-5-nitro-phenyl)morpholine as a yellow solid (2.86 g, 50%); NMR Spectrum (300 MHz, DMSO) 3.30 (m, 4H), 3.72 (m, 4H), 7.24 (m, 1H), 7.38 (m, 1H), 7.52 (m, 1H); followed by 4-(3-morpholin-4-yl-5-nitro-phenyl)morpholine as an orange solid (2.11 g, 29%); Mass Spectrum MH^+ 294.50.

Method 4

3,5-Dinitrobenzenesulfonamide

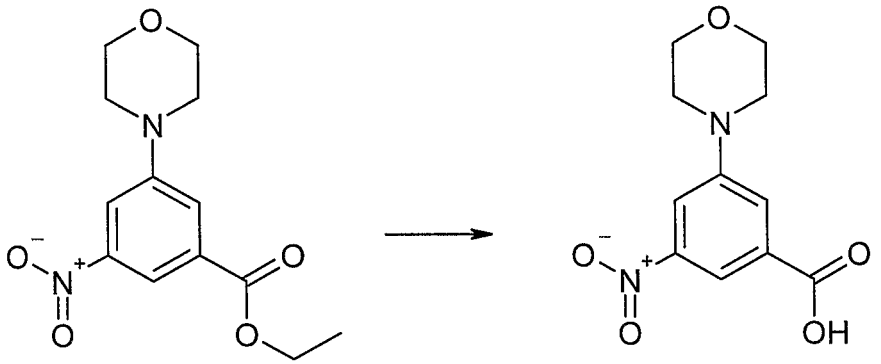


Thionyl chloride (20 ml) was added dropwise to water (70 ml) at 0°C with vigorous stirring. The solution was stirred for 1 hour at 5°C and at 18°C for 50 minutes. Copper (I) chloride (0.16 g) was added to give a pale green solution that was stirred at room temperature for 5 minutes then cooled to –10°C. Separately, 3,5-dinitroaniline (5 g) was added to c. HCl (25 ml) and stirred for 1 hour at room temperature. The solution was cooled to –10°C and treated dropwise with a solution of sodium nitrite (2.26 g) in water (20 ml). The resulting dark orange solution was stirred at –10°C for 10 minutes then added

at –5°C to the solution of copper (I) chloride from the first step over 5 minutes. The reaction was stirred at –5°C for 1 hour then filtered to give a pale pink solid that was dried in vacuo. This solid was added portionwise to a solution of ammonia in methanol (7N, 200 ml) at 0°C and the reaction stirred for 2 hrs then concentrated in vacuo. The resulting solid was triturated with methanol, then water and filtered and dried to give the title compound as a beige solid (2.88 g, 43%); NMR Spectrum (300 MHz, DMSO) 7.86 (br s, 2H), 8.80 (m, 2H), 8.90 (m, 1H); Mass Spectrum M^+ 246.39.

Method 5

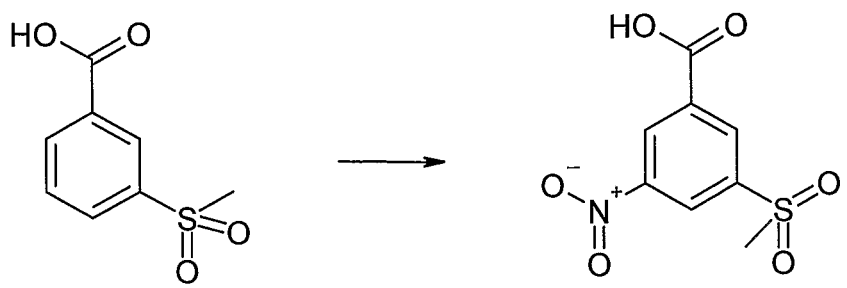
3-Morpholin-4-yl-5-nitro-benzoic acid



Sodium hydroxide (1.8 ml, 2N) was added to a solution of ethyl 3-morpholin-4-yl-5-nitro-benzoate (337 mg – Method 2b) in methanol (10 ml) and THF (10 ml) and stirred for 3 hours at room temperature. Water (3 ml) was added, followed by aq. HCl (1.6 ml, 2N) and the resulting precipitate filtered and dried to give the title compound as a yellow solid (0.23 g, 76%); Mass Spectrum MH^+ 253.44.

Method 6

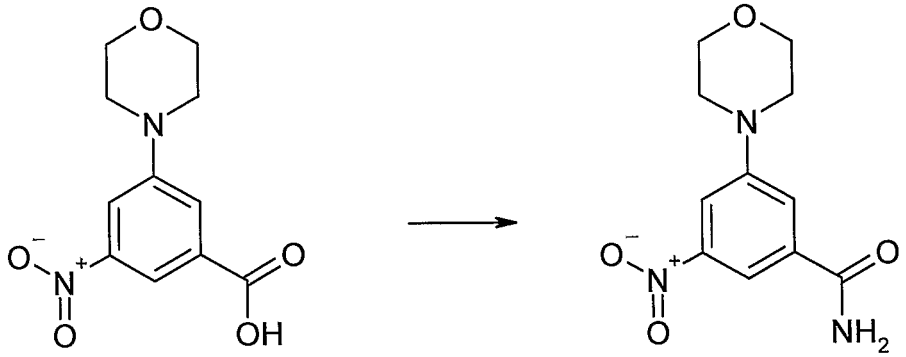
3-Methylsulfonyl-5-nitro-benzoic acid



3-Methylsulfonylbenzoic acid (0.75 g) was added to *c.*sulphuric acid (1.2 ml) and heated to 80°C. Fuming nitric acid (0.6 ml) was added dropwise maintaining the temperature at 80-85 °C, and the reaction stirred at this temperature for 2 hours. The reaction was cooled to room temperature and poured onto 20 ml ice-water to give a white solid which was filtered, washed with water and dried in vacuo to give the title compound as a white solid (0.69 g, 75%); NMR Spectrum (300 MHz, DMSO) 3.44 (s, 3H), 8.75 (t, 1H), 8.84-8.87 (m, 2H).

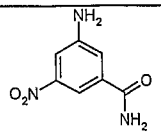
Method 7

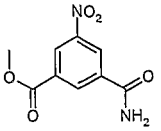
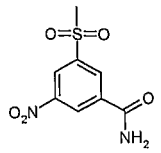
3-Morpholin-4-yl-5-nitro-benzamide



HATU (0.45 g) was added to a solution of 3-morpholin-4-yl-5-nitro-benzoic acid (0.23 g – Method 5), ammonium chloride (146 mg) and DIPEA (0.21 ml) in DMF (1 ml) and the reaction stirred overnight. The solution was concentrated in vacuo and partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated to give the title compound as a yellow solid (0.2 g, 87%); Mass Spectrum MH^+ 252.47.

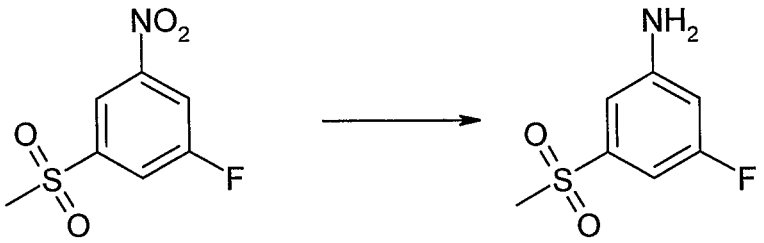
The procedure described above was repeated using the appropriate acid. Thus were obtained the compounds described below:

Method	Name	Structure	Molecular Ion (Observed)	NMR Spectrum (300 MHz, d6-DMSO)
7a	3-amino-5-nitro-benzamide		180.44 (M+)	5.96 (d, 2H), 7.44 (t, 2H), 7.50 (t, 1H), 7.80 (t, 1H), 8.09 (br s, 1H)

Method	Name	Structure	Molecular Ion (Observed)	NMR Spectrum (300 MHz, d6-DMSO)
7b	methyl 3-carbamoyl-5-nitro-benzoate		223.46 (M+)	3.88 (s, 3H), 7.73 (br s, 1H), 8.44 (br s, 1H), 8.64 (m, 1H), 8.72 (m, 1H), 8.85 (m, 1H)
7c	3-methylsulfonyl-5-nitro-benzamide		243.43 (M+)	3.40 (s, 3H), 7.93 (br s, 1H), 8.57 (br s, 1H), 8.77 - 8.80 (m, 2H), 8.97 (t, 1H)

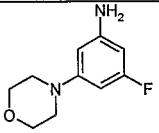
Method 8

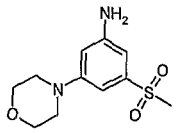
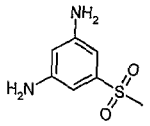
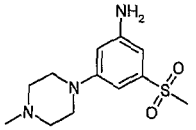
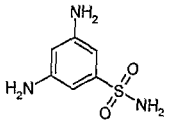
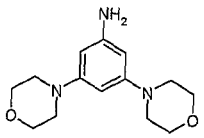
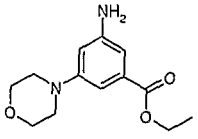
3-Fluoro-5-methylsulfonyl-aniline

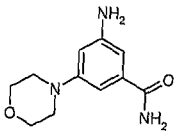
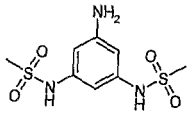
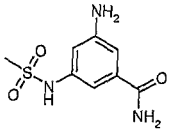
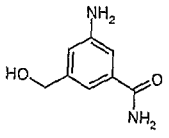
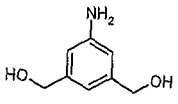


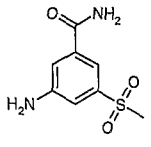
A mixture of 1-fluoro-3-methylsulfonyl-5-nitro-benzene (0.2 g – method 1) and 10% Pd/C (50 mg) in ethanol (20 ml) was stirred under a hydrogen atmosphere overnight. The solution was filtered and concentrated to give the title compound as a pale brown oil (0.18 g, 100%); Mass Spectrum M^+ 189.03.

The procedure described above was repeated using the appropriate nitrobenzene. Thus were obtained the examples described below:

Method	Name	Structure	Molecular Ion (Observed)	NMR Spectrum (300 MHz, d6-DMSO)	Starting material (Method)
8a	3-fluoro-5-morpholin-4-yl-aniline		197.51 (MH+)		3

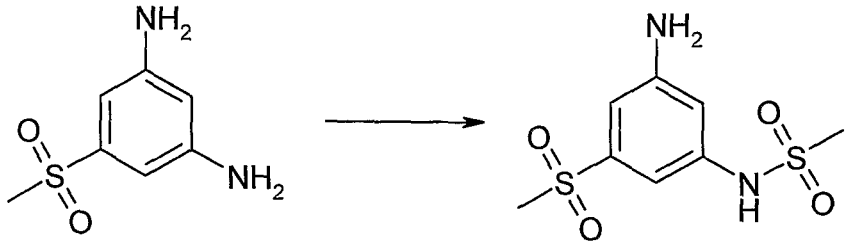
Method	Name	Structure	Molecular Ion (Observed)	NMR Spectrum (300 MHz, d6-DMSO)	Starting material (Method)
8b	3-methylsulfonyl-5-morpholin-4-yl-aniline		257.47 (MH+)		2
8c	5-methylsulfonylbenzene-1,3-diamine		187.46 (MH+)		1a
8d	3-(4-methylpiperazin-1-yl)-5-methylsulfonyl-aniline		270.48 (MH+)		2a
8e	3,5-diaminobenzenesulfonamide		188.45 (MH+)		4
8f	3,5-dimorpholin-4-ylaniline		264.52 (MH+)	2.98 (t, 8H), 3.69 (t, 8H), 4.71 (d, 2H), 5.70 - 5.74 (m, 2H), 5.75 (s, 1H)	3
8g	ethyl 3-amino-5-morpholin-4-yl-benzoate		251.47 (MH+)	1.28 (t, 3H), 3.06 (m, 4H), 3.73 (m, 4H), 4.25 (q, 2H), 5.20 (br s, 2H), 6.40 (m, 1H), 6.70 (m, 2H)	2b

Method	Name	Structure	Molecular Ion (Observed)	NMR Spectrum (300 MHz, d6-DMSO)	Starting material (Method)
8h	3-amino-5-morpholin-4-yl-benzamide		222.54 (MH+)	3.05 (t, 4H), 3.72 (t, 4H), 5.00 (d, 1H), 6.27 (t, 1H), 6.56 (s, 1H), 6.62 (s, 1H), 7.01 (br s, 1H), 7.64 (br s, 1H)	7
8i	3-(hydroxymethyl)-5-methyl-benzenesulfonamide		279.04 (M+)	2.95 (s, 6H), 5.27 (br s, 2H), 6.20 (m, 2H), 6.30 (m, 1H), 9.43 (br s, 2H)	
8j	3-amino-5-methanesulfonamido-benzamide		228.48 (M+)	2.97 (s, 3H), 5.30 (s, 2H), 6.58 (t, 1H), 6.74 - 6.78 (m, 2H), 7.11 (s, 1H), 7.66 (s, 1H), 9.48 (s, 1H)	9b
8k	3-amino-5-(hydroxymethyl)benzamide		166.07 (M+)		10a
8l	[3-amino-5-(hydroxymethyl)phenyl]methanol		154.47 (MH+)	3.25 (1H, under water), 4.29 - 4.37 (m, 4H), 4.93 (t, 3H), 6.41 (s, 3H)	

Method	Name	Structure	Molecular Ion (Observed)	NMR Spectrum (300 MHz, d6-DMSO)	Starting material (Method)
8m	3-amino-5-methylsulfonyl-benzamide		215.47 (MH+)	3.15 (s, 3H), 5.82 (d, 2H), 7.19 (t, 1H), 7.31 - 7.36 (m, 2H), 7.47 (s, 1H), 7.98 (br s, 1H)	7c

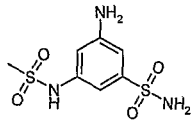
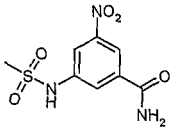
Method 9

N-(3-Amino-5-methylsulfonyl-phenyl)methanesulfonamide



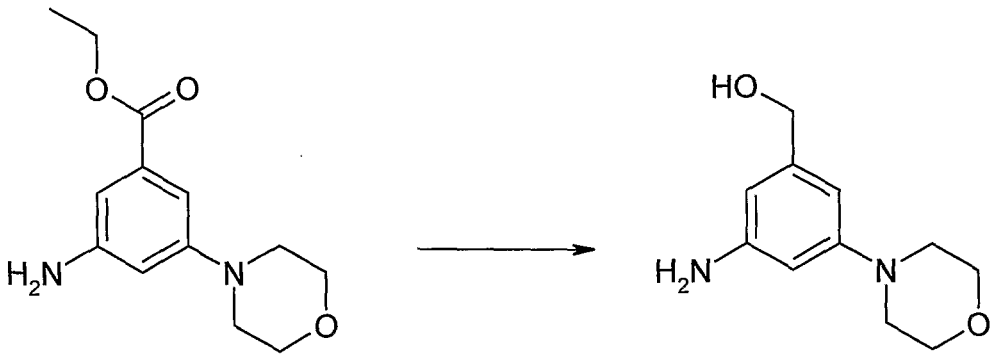
Methanesulfonyl chloride (62 µl) was added to a solution of 5-methylsulfonylbenzene-1,3-diamine (0.15 g – Method 8c) and pyridine (0.33 ml) in DCM (15 ml) and the reaction stirred for two hours at room temperature. The solution was washed with water, dried and concentrated and the residue purified by chromatography to give the title compound as a brown oil (45 mg, 21%); Mass Spectrum MH^+ 265.36.

The procedure described above was repeated using the appropriate aniline. Thus were obtained the compounds described below:

Method	Name	Structure	Molecular Ion (Observed)	NMR Spectrum (300 MHz, d6-DMSO)	Starting Material (Method)
9a	3-amino-5-methanesulfonamido-benzenesulfonamide		266.39 (MH+)		8e
9b	3-methanesulfonamido-5-nitro-benzamide		258.42 (M+)	3.14 (s, 3H), 7.70 (br s, 1H), 8.08 (s, 1H), 8.17 (s, 1H), 8.35 (br s, 1H), 8.43 (s, 1H), 10.46 (s, 1H)	

Method 10

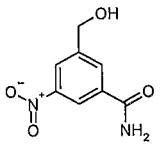
(3-Amino-5-morpholin-4-yl-phenyl)methanol



Lithium aluminium hydride (0.48 ml, 1M in THF) was added dropwise to ethyl 3-amino-5-morpholin-4-yl-benzoate (0.1 g – Method 8g) in THF (3 ml) and the mixture stirred overnight at room temperature. Water (0.1 ml) was added, followed by aqueous sodium hydroxide (0.1 ml, 1M), then magnesium sulfate (1 g) and diethyl ether (10 ml) added. The mixture was stirred at room temperature for 20 minutes then filtered and washed with ether. The filtrate was concentrated in vacuo and the residue purified by chromatography

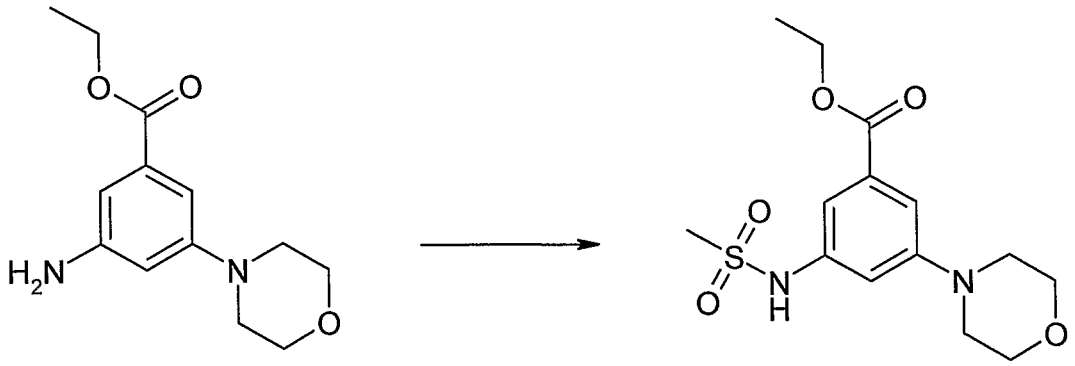
using 0 to 10% methanol in DCM as eluent to give the title compound as an orange solid (80 mg, 96%); NMR Spectrum (300 MHz, DMSO) 2.99 (m, 4H), 3.70 (m, 4H), 4.30 (m, 2H), 4.85 (br s, 2H), 6.02 (m, 1H), 6.07 (s, 1H), 6.11 (s, 1H); Mass Spectrum MH^+ 209.52.

The procedure described above was repeated using the appropriate ester. Thus was obtained the compound described below:

Method	Name	Structure	Molecular Ion (Observed)	NMR Spectrum (300 MHz, d6-DMSO)	Starting material (Method)
10a	3-(hydroxymethyl)-5-nitro-benzamide		195.44 (M+)	4.69 (m, 2H), 5.60 (t, 1H), 7.65 (br s, 1H), 8.27 (m, 1H), 8.34 (m, 2H), 8.58 (m, 1H)	7b

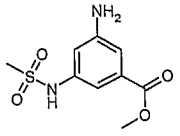
Method 11

Ethyl 3-methanesulfonamido-5-morpholin-4-yl-benzoate



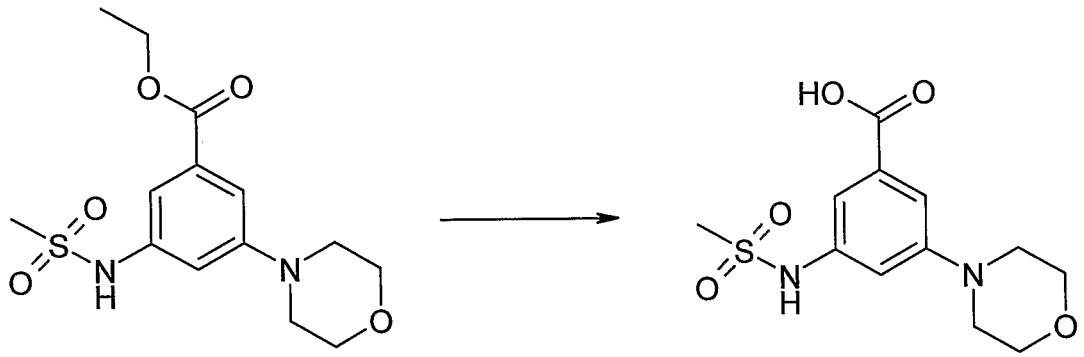
Methanesulfonyl chloride (127 µl) was added to a solution of ethyl 3-amino-5-morpholin-4-yl-benzoate (0.344 g - Method 8g) and pyridine (0.54 ml) in THF (3 ml) and the reaction stirred overnight at room temperature. The solution was concentrated in vacuo and the residue partitioned between 1M HCl and diethyl ether. The organic layer was concentrated and triturated with diethyl ether and iso-hexane to give the title compound as a yellow solid (404 mg, 89%); NMR Spectrum (300 MHz, DMSO) 1.22 (t, 3H), 3.03 (m, 4H), 3.65 (m, 4H), 4.21 (q, 2H), 6.91 (m, 1H), 7.14 (m, 1H), 7.20 (m, 1H), 9.68 (s, 1H); Mass Spectrum MH^+ 329.49.

The procedure described above was repeated using the appropriate aniline. Thus was obtained the example described below:

Method	Name	Structure	Molecular Ion (Observed)	NMR Spectrum (300 MHz, d6-DMSO)
11a	methyl 3-amino-5-methanesulfonamido-benzoate		245.41 (MH+)	2.94 (s, 3H), 3.80 (s, 3H), 5.50 (br s, 2H), 6.69 (m, 1H), 6.93 (m, 1H), 6.98 (m, 1H), 9.60 (br s, 1H)

Method 12

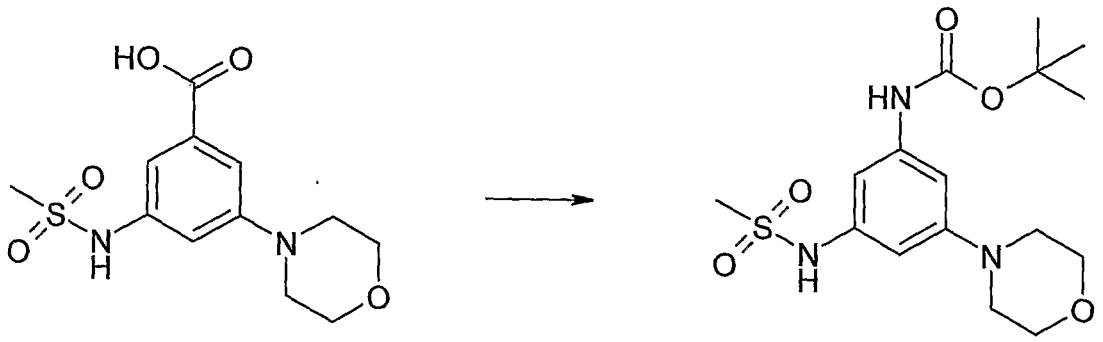
3-Methanesulfonamido-5-morpholin-4-yl-benzoic acid



Lithium hydroxide (71 mg) and ethyl 3-methanesulfonamido-5-morpholin-4-yl-benzoate (404 mg – method 11) in THF (3 ml) and water (0.1 ml) were stirred for 48 hours then concentrated in vacuo. The residue was dissolved in water (5 ml) and *p*H adjusted to 5. The resulting precipitate was filtered and dried to give the title compound as a yellow solid (0.26 g, 71%); Mass Spectrum MH^+ 301.47.

Method 13

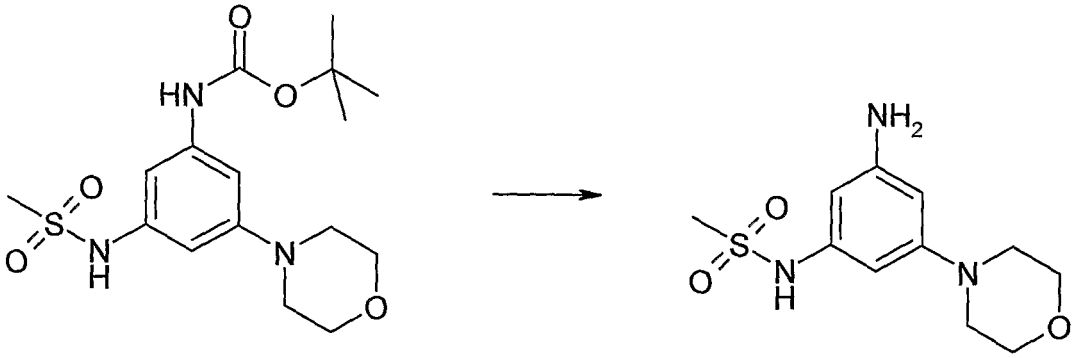
Tert-Butyl N-(3-methanesulfonamido-5-morpholin-4-yl-phenyl)carbamate



Diphenylphosphoryl azide (0.224 ml) was added to a solution of 3-methanesulfonamido-5-morpholin-4-yl-benzoic acid (0.26 g – method 12) and DIPEA (0.18 ml) in *tert*-butanol (10 ml) and the reaction heated at 80°C for 5 hours. The reaction was concentrated in vacuo and the residue purified by chromatography using 0 to 100% ethyl acetate in iso-hexane then 5% methanol in DCM as eluent to give the title compound as a white foam (150 mg, 35%); Mass Spectrum MH^+ 372.49.

Method 14

N-(3-Amino-5-morpholin-4-yl-phenyl)methanesulfonamide

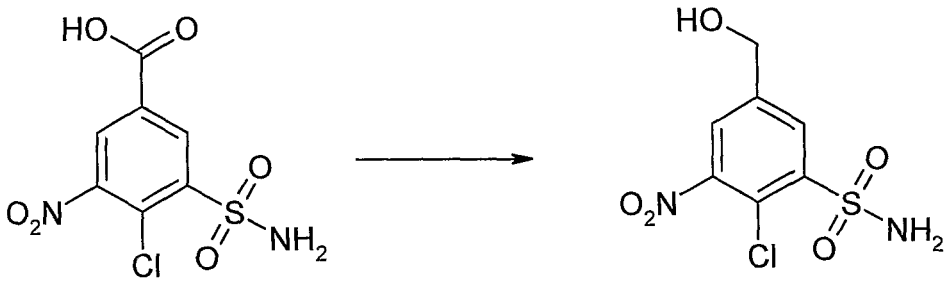


Tert-butyl N-(3-methanesulfonamido-5-morpholin-4-yl-phenyl)carbamate (0.15 g – method 13) and c.HCl (3 ml) in methanol (5 ml) were heated at 70°C for 5 hours then cooled and concentrated in vacuo. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate and combined organic layers dried and concentrated and the residue purified by chromatography using ethyl acetate as eluent followed by trituration with ethyl acetate – diethyl ether – iso-hexane to give the title compound as a

white solid (24 mg, 22%); NMR Spectrum (300 MHz, DMSO) 2.92 (s, 3H), 2.96 (m, 4H), 3.70 (m, 4H), 5.90 (m, 1H), 6.00 (m, 2H), 9.20 (br s, 1H); Mass Spectrum MH^+ 272.46.

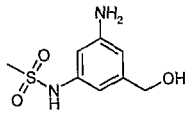
Method 15

2-Chloro-5-(hydroxymethyl)-3-nitro-benzenesulfonamide



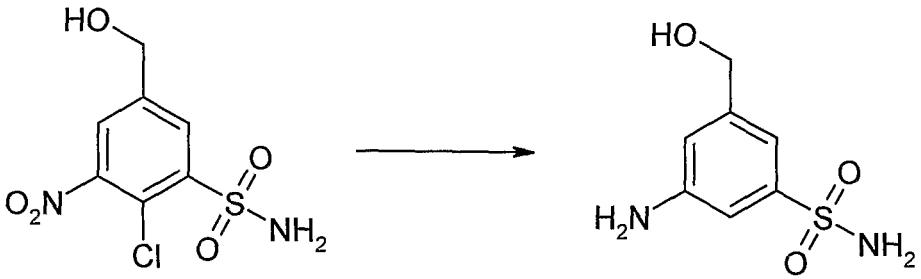
Borane in THF (12 ml, 1M) was added dropwise to 4-chloro-3-nitro-5-sulfamoyl-benzoic acid (1.6 g) in THF (30 ml) and the reaction stirred overnight at room temperature. Methanol was added dropwise and the reaction mixture stirred for 20 minutes at room temperature. The reaction mixture was concentrated in vacuo and the residue partitioned between water and ethyl acetate, dried and concentrated. The residue was purified by chromatography using 0 to 100% ethyl acetate in iso-hexane then 5% methanol in DCM as eluent to give the title compound as a yellow solid (2.5g, >100%); NMR Spectrum (300 MHz, DMSO) 4.52 (m, 2H), 5.60 (t, 1H), 7.82 (br s, 2H), 8.04 (s, 1H), 8.14 (s, 1H); Mass Spectrum MH^+ 265.33.

The procedure described above was repeated using, in this case, the appropriate methyl benzoate ester (rather than benzoic acid). Thus was obtained the compound described below:

Method	Name	Structure	Molecular Ion (Observed)	NMR Spectrum (300 MHz, d6-DMSO)	Starting Material
15a	N-[3-amino-5-(hydroxymethyl) phenyl] methanesulfonamide			2.91 (s, 3H), 4.29 (d, 2H), 4.98 (t, 1H), 5.10 (br s, 2H), 6.29 (s, 1H), 6.34 (m, 2H), 9.30 (s, 1H)	

Method 16

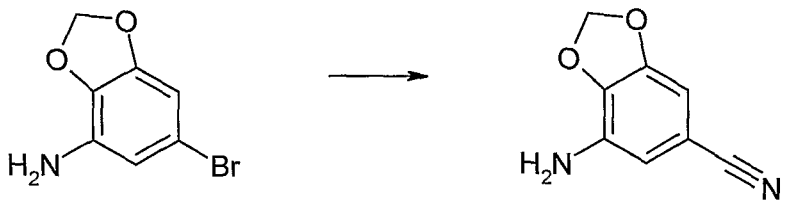
3-(Hydroxymethyl)-5-methyl-benzenesulfonamide



A mixture of 2-chloro-5-(hydroxymethyl)-3-nitro-benzenesulfonamide (2.5 g - method 15) and 10% Pd/C (200 mg) in ethanol (200 ml) was stirred under a hydrogen atmosphere at 50°C overnight. The solution was cooled, filtered and concentrated, and the residue purified by chromatography using 0 to 25% methanol in DCM as eluent to give the title compound as a white solid (509 mg, 51%); NMR Spectrum (300 MHz, DMSO) 4.40 (m, 2H), 5.19 (t, 1H), 5.44 (br s, 2H), 6.68 (s, 1H), 6.90 (m, 1H), 6.94 (s, 1H), 7.09 (br s, 2H); Mass Spectrum MH^+ 203.

Method 17

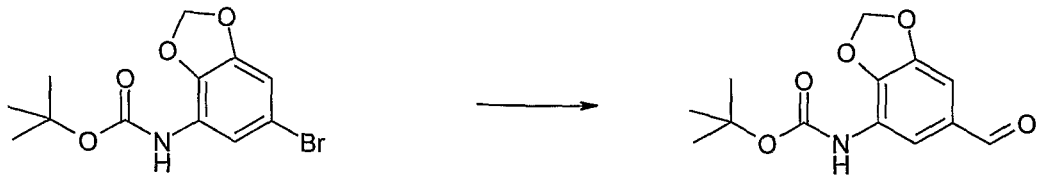
7-Aminobenzo[1,3]dioxole-5-carbonitrile



Zinc powder (125 mg), zinc cyanide (560 mg), tris(dibenzylideneacetone)dipalladium(0) (290 mg) and 1,1'-bis(diphenylphosphino)ferrocene (350 mg) were added to a solution of 6-bromobenzo[1,3]dioxol-4-amine (1 g, prepared as described in WO2004005284) and DIPEA (0.69 ml) in DMF (30 ml) and the reaction heated at 110°C overnight. The solution was concentrated in vacuo and the residue partitioned between ethyl acetate and saturated aqueous sodium bicarbonate and filtered. Combined organic extracts were dried and concentrated to give a brown oil that was purified by chromatography using ethyl acetate:iso-hexane (80% to 50%) as eluent to give the title compound as a yellow solid (548 mg, 73%); NMR Spectrum (300 MHz, DMSO) 5.42 (br s, 2H), 6.06 (s, 2H), 6.66 (s, 2H); Mass Spectrum $M\text{-}H^+$ 161.

Method 18

Tert-butyl N-(6-formylbenzo[1,3]dioxol-4-yl)carbamate



n-Butyl Lithium (9.96 ml, 2.5M in hexanes) was added dropwise to a solution of *tert*-butyl N-(6-bromobenzo[1,3]dioxol-4-yl)carbamate (3 g, prepared as described in WO2004005284) in THF (60 ml) at –78°C and the mixture was stirred for 20 minutes. DMF (0.9 ml) was added and the solution allowed to warm to room temperature. Saturated aqueous sodium bicarbonate solution (75 ml) was added and the solution

extracted with ethyl acetate, dried and concentrated. The residue was purified by chromatography using hexane to hexane–ethyl acetate (2:3) as eluent to give the title compound as a white solid (1.9 g, 76%); NMR Spectrum (300 MHz, DMSO) 1.45 (s, 9H), 6.18 (s, 2H), 7.17 (d, 1H), 7.68 (s, 1H), 9.14 (s, 1H), 9.78 (s, 1H); Mass Spectrum M^+ 265.09.

Method 19

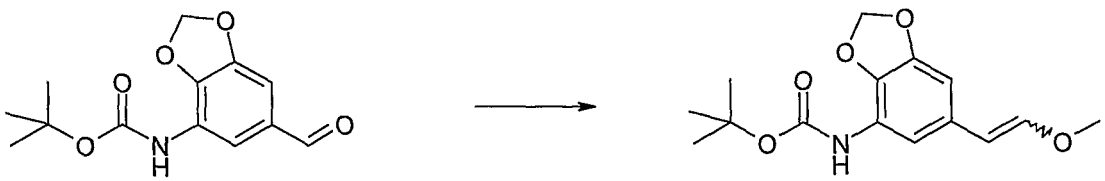
Tert-butyl N-[6-(hydroxymethyl)benzo[1,3]dioxol-4-yl]carbamate



Sodium borohydride (306 mg) was added to a solution of *tert*-butyl N-(6-formylbenzo[1,3]dioxol-4-yl)carbamate (1.79 g – method 18) in methanol (50 ml) and the reaction stirred at room temperature for 2 hours then concentrated in vacuo. The residue was partitioned between water and ethyl acetate, dried and concentrated to give the title compound as a white foam (1.8 g, 100%); NMR Spectrum (300 MHz, DMSO) 1.43 (s, 9H), 4.35 (m, 2H), 5.08 (t, 1H), 5.96 (s, 2H), 6.62 (s, 1H), 6.89 (s, 1H), 8.75 (s, 1H).

Method 20

Tert-butyl N-[6-[(E/Z)-2-methoxyethenyl]benzo[1,3]dioxol-4-yl]carbamate

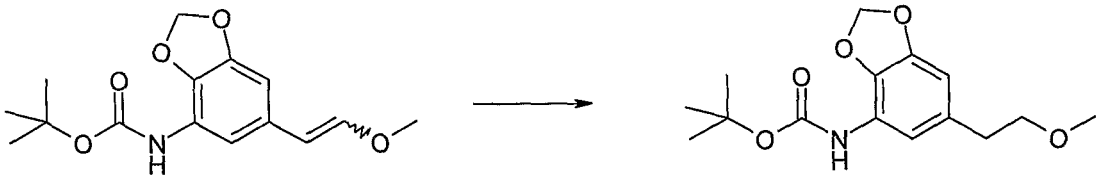


Potassium *tert*-butoxide (0.75 ml, 1M in THF) was added dropwise to a stirred suspension of the (methoxymethyl)triphenylphosphonium chloride (288 mg) in THF (3 ml) cooled in an ice bath. After stirring the red solution at room temperature for 30 minutes, *tert*-butyl N-(6-formylbenzo[1,3]dioxol-4-yl)carbamate (100 mg – method 18) in THF (3 ml) was

added and the reaction stirred at room temperature for 12 hours. The reaction was partitioned between saturated aqueous ammonium chloride solution and diethyl ether. Combined organic extracts were washed with water, dried and concentrated and the residue purified by chromatography using iso-hexane to iso-hexane – 10% ethyl acetate as eluent to give the title compound as a pale yellow oil (65 mg, 59%); NMR Spectrum (300 MHz, DMSO) 1.44 (d, 9H), 3.60 (s, 1.5H), 3.72 (s, 1.5H), 5.11 (d, 0.5H), 5.74 (d, 0.5H), 5.95 (d, 2H), 6.18 (d, 0.5H), 6.74 - 6.77 (d, 1H), 6.95 - 6.97 (m, 1H), 7.10 (d, 0.5H), 8.72 (d, 1H); Mass Spectrum M^+ 292.43.

Method 21

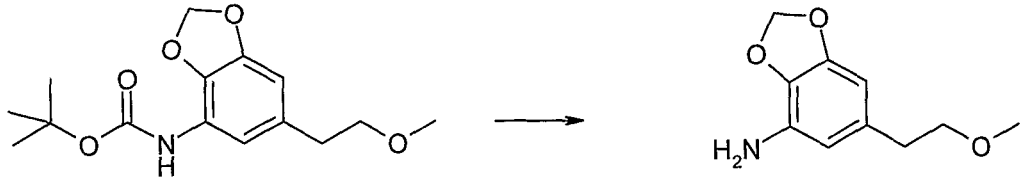
Tert-butyl N-[6-(2-methoxyethyl)benzo[1,3]dioxol-4-yl]carbamate



Tert-butyl N-[6-[(E)-2-methoxyethenyl]benzo[1,3]dioxol-4-yl]carbamate (0.9 g – method 20) and 10% Pd/C (90 mg) in ethanol (90 ml) were stirred under an atmosphere of hydrogen overnight. The solution was filtered and concentrated in vacuo to give the title compound as a pale brown oil (0.8 g, 88%); NMR Spectrum (300 MHz, DMSO) 1.44 (s, 9H), 2.68 (t, 2H), 3.30 (s, 3H), 3.40 - 3.47 (m, 2H), 5.95 (s, 2H), 6.58 - 6.59 (m, 1H), 6.76 (s, 1H), 8.72 (s, 1H); Mass Spectrum M-H^+ 294.5.

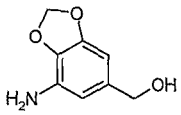
Method 22

6-(2-Methoxyethyl)benzo[1,3]dioxol-4-amine



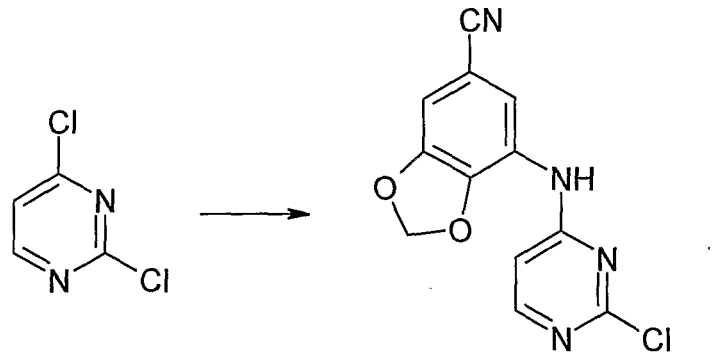
Tert-butyl N-[6-(2-methoxyethyl)benzo[1,3]dioxol-4-yl]carbamate (0.8 g – method 21) and c.HCl (0.25 ml) in methanol (10 ml) were heated at 70°C for 2 hours then cooled and concentrated in vacuo. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate and combined organic layers dried and concentrated and the residue purified by chromatography using 1:1 DCM-ethyl acetate as eluent to give the title compound as a pale brown oil (0.4 g, 76%); NMR Spectrum (300 MHz, DMSO) 3.29 (s, 3H), 3.44 (t, 2H), 4.79 (d, 2H), 5.84 (s, 2H), 6.07 (s, 1H), 6.11 (s, 1H); Mass Spectrum MH^+ 196.49.

The procedure described above was repeated using the appropriate *tert*-butyl carbamate. Thus was obtained the compound described below:

Method	Name	Structure	Molecular Ion (Observed)	NMR Spectrum (300 MHz, d6-DMSO)	Starting Material (Method)
22a	(7-aminobenzo [1,3]dioxol-5-yl)methanol		168.46 (MH+)	4.27 (m, 2H), 4.83 (m, 1H), 4.92 (t, 1H), 5.86 (s, 2H), 6.13 (s, 1H), 6.24 (s, 1H)	19

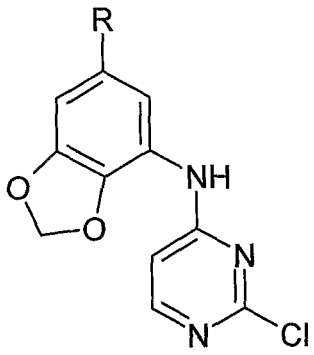
Method 23

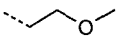
7-[(2-Chloropyrimidin-4-yl)amino]benzo[1,3]dioxole-5-carbonitrile



Sodium hydride (67 mg, 60% dispersion in mineral oil) was added to 7-aminobenzo[1,3]dioxole-5-carbonitrile (109 mg – method 17) in DMA (1 ml) at room temperature. 2,4-Dichloropyrimidine (100 mg) was added and the reaction stirred overnight. The reaction was quenched cautiously with water and the solution concentrated. The residue was triturated with water to give a solid which was filtered and dried in vacuo to give the title compound as a beige solid (83 mg, 45%); Mass Spectrum MH^+ 275.37.

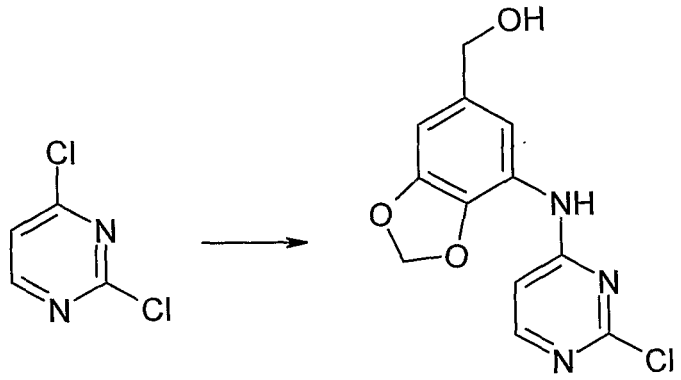
The procedure described above was repeated using the appropriate aniline. Thus were obtained the compounds described below:



Method	Name	R	Molecular Ion (Observed)	Starting Material (method)
23a	N-(6-bromobenzo[1,3]dioxol-4-yl)-2-chloro-pyrimidin-4-amine		330.29 (MH+)	
23b	2-chloro-N-[6-(2-methoxyethyl)benzo[1,3]dioxol-4-yl]pyrimidin-4-amine		308.42 (MH+)	22

Method 24

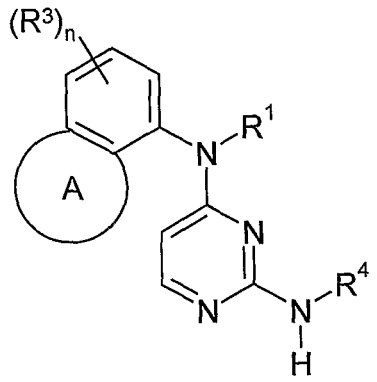
[7-[(2-Chloropyrimidin-4-yl)amino]benzo[1,3]dioxol-5-yl]methanol



A mixture of DIPEA (0.07 ml), 2, 4-dichloropyrimidine (50 mg) and (7-aminobenzo[1,3]dioxol-5-yl)methanol (56 mg – method 22a) in n-butanol (1 ml) was heated at 115°C overnight then concentrated in vacuo. The residue was partitioned between ethyl acetate and water, and the organic solution concentrated. The residue was purified by chromatography using ethyl acetate as eluent to give the title compound as a white solid (37 mg, 39%); Mass Spectrum MH^+ 280.42.

Claims

1. A compound of formula (I)



(I)

where **R**[1] is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, or C_{2-6}alkynyl, wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by one or more substituent groups selected from cyano, nitro, $-OR^2$, $-NR^{2a}R^{2b}$, $-C(O)NR^{2a}R^{2b}$, or $-N(R^{2a})C(O)R^2$, halo or haloC_{1-4}alkyl, where R^2, R^{2a} and R^{2b} are selected from hydrogen or C_{1-6}alkyl such as methyl, or R^{2a} and R^{2b} together with the nitrogen atom to which they are attached may form a 5 or 6-membered heterocyclic ring, which optionally contains an additional heteroatom selected from N, O or S;

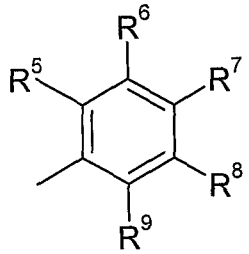
ring **A** is fused 5 or 6-membered carbocyclic or heterocyclic ring, which is saturated or unsaturated, and is optionally substituted on any available carbon atom by one or more substituent groups selected from halo, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, $-S(O)_z-C_{1-6}$alkyl (where z is 0, 1 or 2), or $-NR^aR^b$ (where R^a and R^b are each independently selected from hydrogen, C_{1-4}alkyl, or C_{1-4}alkylcarbonyl), and where any nitrogen atoms in the ring are optionally substituted by a C_{1-6}alkyl or C_{1-6}alkylcarbonyl;
n is 0, 1, 2 or 3

and each group **R**[3] is independently selected from halo, trifluoromethyl, cyano, nitro or a group of sub-formula (i) :

$$-X^1-R^{11} \qquad \text{(i)}$$

where $\mathbf{X^1}$ is selected from a direct bond or O, S, SO, SO_2, OSO_2, NR^{13}, CO, $CH(OR^{13})$, $CONR^{13}$, $N(R^{13})CO$, $SO_2N(R^{13})$, $N(R^{13})SO_2$, $C(R^{13})_2O$, $C(R^{13})_2S$, $C(R^{13})_2N(R^{13})$ and $N(R^{13})C(R^{13})_2$, wherein $\mathbf{R^{13}}$ is hydrogen or C_{1-6}alkyl and $\mathbf{R^{11}}$ is selected from hydrogen, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}cycloalkyl, aryl or heterocyclyl, C_{3-8}cycloalkylC_{1-6} alkyl, arylC_{1-6} alkyl or heterocyclylC_{1-6}alkyl, any of which may be optionally substituted with one or more groups selected from halo, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, C_{1-6}alkoxy, C_{2-6}alkenyoxyl, C_{2-6}alkynyloxy, C_{1-6}alkylthio, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, C_{1-6}alkylamino, di-(C_{1-6}alkyl)amino, C_{1-6}alkoxycarbonyl, N-C_{1-6}alkylcarbamoyl, N, N-di-(C_{1-6}alkyl)carbamoyl, C_{2-6}alkanoyl, C_{2-6}alkanoyloxy, C_{2-6}alkanoylamino, N-C_{1-6}alkyl-C_{2-6}alkanoylamino, C_{3-6}alkenoylamino, N-C_{1-6}alkyl-C_{3-6}alkenoylamino, C_{3-6}alkynoylamino, N-C_{1-6}alkyl- C_{3-6}alkynoylamino, N-C_{1-6}alkylsulphamoyl, N,N-di-(C_{1-6}alkyl)sulphamoyl, C_{1-6}alkanesulphonylamino and N-C_{1-6}alkyl-C_{1-6}alkanesulphonylamino, and any heterocyclyl group within R^{11} optionally bears 1 or 2 oxo or thioxo substituents; and

$\mathbf{R^4}$ is a group of sub-formula (iii)



(iii)

where $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$ and $\mathbf{R^9}$ are each independently selected from:

(i) hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl), heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) and wherein any aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl), heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) groups are optionally substituted on any available carbon atoms by halo, hydroxy, cyano, amino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino, and any nitrogen atoms present in a

heterocyclyl group may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl, and where any sulphur atoms may be optionally oxidised to a sulphur oxide;

(ii) a group of sub-formula (iv):

$$-X^2-R^{14} \qquad \text{(iv)}$$

where $\mathbf{X^2}$ is selected from O, NR^{16}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{16})$, $CON(R^{16})$, $N(R^{16})CO$, $-N(R^{16})C(O)N(R^{16})-$, $-N(R^{16})C(O)O-$, $SON(R^{16})$, $N(R^{16})SO$, $SO_2N(R^{16})$, $N(R^{16})SO_2$, $C(R^{16})_2O$, $C(R^{16})_2S$ and $N(R^{16})C(R^{16})_2$, where each R^{16} is independently selected from hydrogen or C_{1-6}alkyl,

$\mathbf{R^{14}}$ is hydrogen, C_{1-6} alkyl, trifluoromethyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, or a 4- to 8-membered mono or bicyclic heterocyclyl ring (including 5 or 6 membered heteroaryl rings) or 4- to 8-membered mono or bicyclic heterocyclyl-C_{1-6}alkyl groups (including 5 or 6 membered heteroaryl-C_{1-6}alkyl groups) and wherein any aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl), heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) groups are optionally substituted on any available carbon atoms by oxo, halo, cyano, amino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino and any nitrogen atoms present in the heterocyclyl moieties may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl, and where any sulphur atoms may be optionally oxidised to a sulphur oxide;

iii) a group of sub-formula (v):

$$-X^3-R^{15}-Z \qquad \text{(v)}$$

where $\mathbf{X^3}$ is a direct bond or is selected from O, NR^{17}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{17})$, $CON(R^{17})$, $N(R^{17})CO$, $-N(R^{17})C(O)N(R^{17})-$, $-N(R^{17})C(O)O-$, $SO_2N(R^{17})$, $N(R^{17})SO_2$, $C(R^{17})_2O$, $C(R^{17})_2S$ and $N(R^{17})C(R^{17})_2$, where each R^{17} is independently selected from hydrogen or C_{1-6}alkyl;

$\mathbf{R^{15}}$ is a C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene, arylene, C_{3-12} carbocyclyl, heterocyclyl (including heteroaryl), any of which may be optionally substituted by one or more groups selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, amino, C_{1-6}alkylamino or di-(C_{1-6}alkyl)amino;

Z is halo, trifluoromethyl, cyano, nitro, aryl, C_{3-12} carbocyclyl or heterocyclyl (including heteroaryl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl and C_{1-6}alkoxy and wherein any heterocyclyl group within Z optionally bears 1 or 2 oxo substituents,

or Z is a group of sub-formula (vi)

$$-X^4-R^{18} \qquad \text{(vi)}$$

where $\mathbf{X^4}$ is selected from O, NR^{19}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{19})$, $CON(R^{19})$, $N(R^{19})CO$, $SO_2N(R^{19})$, $-N(R^{19})C(O)N(R^{19})-$, $-N(R^{19})C(O)O-$ $N(R^{19})SO_2$, $C(R^{19})_2O$, $C(R^{19})_2S$ and $N(R^{19})C(R^{19})_2$, where each R^{19} is independently selected from hydrogen or C_{1-6}alkyl; and R^{18} is selected from hydrogen, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl) or heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl and C_{1-6}alkoxy, and wherein any heterocyclyl group within R^{18} optionally bears 1 or 2 oxo substituents;

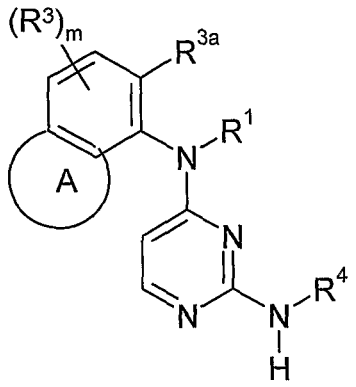
or

(iv) R^5 and R^6, R^6 and R^7, R^7 and R^8 or R^8 and R^9 are joined together to form a fused 5, 6 or 7-membered ring, wherein said ring is unsaturated or partially or fully saturated and is optionally substituted on any available carbon atom by halo, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, amino, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino, and said ring may contain one or more heteroatoms selected from oxygen, sulphur or nitrogen, where sulphur atoms may be optionally oxidised to a sulphur oxide, where any CH_2 groups may be substituted by a C(O) group, and where nitrogen atoms, depending upon valency considerations, may be substituted by a group R^{21}, where R^{21} is selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl;

or a pharmaceutically acceptable salt thereof,

with the proviso that if Ring A, together with the phenyl ring to which attached, forms an indazol-4-yl group, then R^1 is not hydrogen.

2. A compound of formula (IA)



(IA)

where A, R^1, R^3 and R^4 are as defined in claim 1, R^{3a} is a group R^3 as defined in claim 1, and m is 0, 1 or 2.

3. A compound according to claim 2 wherein R^{3a} is halo.

4. A compound according to claim 2 or claim 3 where m is 0.

5. A compound according to any one of claims 1 to 4 wherein Ring A is selected from $-CR^{22}=CR^{22}-CR^{22}=CR^{22}-$, $-N=CR^{22}-CR^{22}=CR^{22}-$, $-CR^{22}=N-CR^{22}=CR^{22}-$, $-CR^{22}=CR^{22}-N=CR^{22}-$, $-CR^{22}=CR^{22}-CR^{22}=N-$, $-N=CR^{22}-N=CR^{22}-$, $-CR^{22}=N-CR^{22}=N-$, $-N=CR^{22}-CR^{22}=N-$, $-N=N-CR^{22}=CR^{22}-$, $-CR^{22}=CR^{22}-N=N-$, $-CR^{22}=CR^{22}-O-$, $-O-CR^{22}=CR^{22}-$, $-CR^{22}=CR^{22}-S-$, $-S-CR^{22}=CR^{22}-$, $-CR^{22}H-CR^{22}H-O-$, $-O-CR^{22}H-CR^{22}H-$, $-CR^{22}H-CR^{22}H-S-$, $-S-CR^{22}H-CR^{22}H-$, $-O-CR^{22}H-O-$, $-O-CF_2-O-$, $-O-CR^{22}H-CR^{22}H-O-$, $-S-CR^{22}H-S-$, $-S-CR^{22}H-CR^{22}H-S-$, $-CR^{22}=CR^{22}-NR^{20}-$, $-NR^{20}-CR^{22}=CR^{22}-$, $-CR^{22}H-CR^{22}H-NR^{20}-$, $-NR^{20}-CR^{22}H-CR^{22}H-$, $-N=CR^{22}-NR^{20}-$, $-NR^{20}-CR^{22}=N-$, $-NR^{20}-CR^{22}H-NR^{20}-$, $-OCR^{22}=N-$, $-N=CR^{22}-O-$, $-S-CR^{22}=N-$, $-N=CR^{22}-S-$, $-O-CR^{22}H-NR^{20}-$, $-NR^{20}-CR^{22}H-O-$, $-S-CR^{22}H-NR^{20}-$, $-NR^{20}-CR^{22}H-S-$, $-O-N=CR^{22}-$, $-CR^{22}=N-O-$, $-S-N=CR^{22}-$, $-CR^{22}=N-S-$, $-O-NR^{20}-CR^{22}H-$, $-CR^{22}H-NR^{20}-O-$, $-S-NR^{20}-CR^{22}H-$, $-CR^{22}H-NR^{20}-S-$, $-NR^{20}-N=CR^{22}-$, $-CR^{22}=N-NR^{20}-$, $-NR^{20}-NR^{20}-CR^{22}H-$, $-CR^{22}H-NR^{20}-NR^{20}-$, $-N=N-NR^{20}-$, or $-NR^{20}-N=N-$,

where each R^{20} is independently selected from hydrogen, C_{1-4}alkyl or C_{1-4}alkylcarbonyl, and where each R^{22} is independently selected from hydrogen, halo, cyano, hydroxy,

C_{1-4}alkyl, C_{1-4}alkoxy, -$S(O)_z$-C_{1-4}alkyl (where z is 0, 1 or 2), or –NR^aR^b (where R^a and R^b are each independently selected from hydrogen, C_{1-2}alkyl, or C_{1-2}alkanoyl).

6. A compound according to any one of claims 1 to 4, wherein Ring A is selected from Ring A is selected from -O-CR^{22}H-O-, -O-CF_2-O-, -OCR^{22}=N-, -N=CR^{22}-O-, -S-CR^{22}=N-, -N=CR^{22}-S-, -NR^{20}-N=CR^{22}-, or -CR^{22}=N-NR^{20}-, and each R^{20} is independently selected from hydrogen, or C_{1-2}alkyl, and each R^{22} is independently selected from hydrogen, halo, or methyl.

7. A compound according to any one of claims 1 to 6, wherein R^1 is hydrogen or a C_{1-2}alkyl group, which is optionally substituted with one or more substituents selected from cyano, –OR^2, –$NR^{2a}R^{2b}$, -C(O)$NR^{2a}R^{2b}$, or -N(R^{2a})C(O)R^2, halo or haloC_{1-4}alkyl, wherein R^2, R^{2a} and R^{2b} are selected from hydrogen or C_{1-4}alkyl.

8. A compound according to any one of claims 1 to 6, wherein R^1 is methyl.

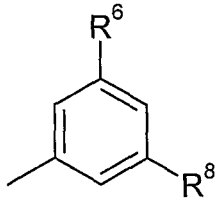
9. A compound according to any one of the preceding claims, wherein each $\mathbf{R^3}$ group present is independently selected from halo, trifluoromethyl, cyano, nitro or a group of sub-formula (i) :

$$-X^1\text{-}R^{11} \qquad \text{(i)}$$

where $\mathbf{X^1}$ is selected from a direct bond or O, $CONR^{13}$, wherein $\mathbf{R^{13}}$ is hydrogen or C_{1-6}alkyl and $\mathbf{R^{11}}$ is selected from hydrogen or C_{1-4}alkyl, which may be optionally substituted with one or more C_{1-2}alkoxy groups.

10. A compound according to claim 1 or any one of claims 5 to 9, wherein n is 0 or 1.

11. A compound according to any one of the preceding claims wherein R^4 is a group of sub-formula (iiib)



(iiib)

wherein at least one of R^6 and R^8 is a 5 or 6-membered nitrogen linked heterocyclic ring and the other is independently selected from:

(a) hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, heterocyclyl (including heteroaryl), and wherein any aryl or heterocyclyl (including heteroaryl) groups are optionally substituted on any available carbon atoms by halo, hydroxy, cyano, amino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, and any nitrogen atoms present in the heterocyclyl moieties may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl;

(b) a group of sub-formula (iv):

$$-X^2-R^{14} \qquad \text{(iv)}$$

where X^2 is selected from O, NR^{16}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{16})$, $CON(R^{16})$, $N(R^{16})CO$, $SON(R^{16})$, $N(R^{16})SO$, $SO_2N(R^{16})$, and $N(R^{16})SO_2$, where each R^{16} is independently selected from hydrogen or C_{1-6}alkyl,

R^{14} is hydrogen, C_{1-6} alkyl, trifluoromethyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, or a 4- to 8-membered mono or bicyclic heterocyclyl ring (including 5 or 6 membered heteroaryl rings) and wherein any aryl, C_{3-12} carbocyclyl, heterocyclyl (including heteroaryl) groups are optionally substituted on any available carbon atoms by oxo, halo, cyano, amino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino and any nitrogen atoms present in the heterocyclyl moieties may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl, and where any sulphur atoms may be optionally oxidised to a sulphur oxide;

(c) a group of sub-formula (v) is

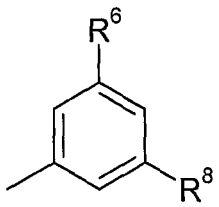
$$-X^3-R^{15}-Z \qquad (v)$$

where X^3 is a direct bond or is selected from O, NR^{17}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CON(R^{17})$, $N(R^{17})CO$, $SO_2N(R^{17})$, and $N(R^{17})SO_2$, where each R^{17} is independently selected from hydrogen or C_{1-6}alkyl; R^{15} is a C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene, arylene, C_{3-12} carbocyclyl, heterocyclyl (including heteroaryl), any of which may be optionally substituted by one or more groups selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, amino, C_{1-6}alkylamino or di-(C_{1-6}alkyl)amino; Z is halo, trifluoromethyl, cyano, nitro, aryl, or heterocyclyl (including heteroaryl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl and C_{1-6}alkoxy and wherein any heterocyclyl group within Z optionally bears 1 or 2 oxo substituents, or Z is a group of sub-formula (vi)

$$-X^4-R^{18} \qquad (vi)$$

where X^4 is selected from O, NR^{19}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CON(R^{19})$, $N(R^{19})CO$, $SO_2N(R^{19})$, and $N(R^{19})SO_2$, where each R^{19} is independently selected from hydrogen or C_{1-6}alkyl; and R^{18} is selected from hydrogen, C_{1-6} alkyl, aryl, or heterocyclyl (including heteroaryl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl, and C_{1-6}alkoxy, and wherein any heterocyclyl group within R^{18} optionally bears 1 or 2 oxo substituents.

12. A compound according to any one of the preceding claims, wherein R^4 is a group of sub-formula (iiib)



(iiib)

wherein at least one of R^6 and R^8 is morpholin-4yl and the other is independently selected from:

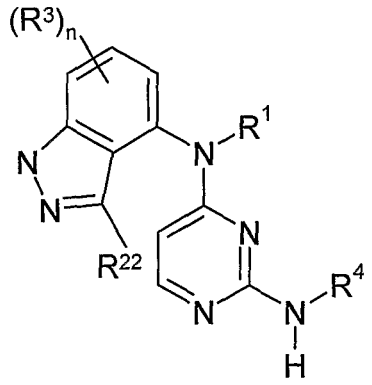
(a) hydrogen, halo, trifluoromethyl, cyano, C_{1-4} alkyl, phenyl, a 5 or 6-membered heterocyclyl (including heteroaryl) comprising one or more heteroatoms selected from N, O or S,
and wherein any C_{1-4} alkyl, aryl or heterocyclyl (including heteroaryl) groups are optionally substituted on any available carbon atoms by halo, hydroxy, cyano, amino, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkoxy, and any nitrogen atoms present in the heterocyclyl moieties may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-4}alkyl or C_{1-4}alkylcarbonyl; or

(b) a group of sub-formula (iv):

$$-X^2-R^{14} \qquad \text{(iv)}$$

where X^2 is selected from O, NR^{16}, S, SO, SO_2, OSO_2, CO, $CON(R^{16})$, $N(R^{16})CO$, $SON(R^{16})$, $N(R^{16})SO$, $SO_2N(R^{16})$, and $N(R^{16})SO_2$, where each R^{16} is independently selected from hydrogen or C_{1-4}alkyl,
R^{14} is hydrogen, or C_{1-4}alkyl;

13. A compound according to claim 1, wherein said compound has the general structural formulae (ID)



(ID)

wherein R^1 is a C_{1-6}alkyl group, which is optionally substituted with one or more substituents selected from cyano, $-OR^2$, $-NR^{2a}R^{2b}$, where R^2, R^{2a} and R^{2b} are selected from hydrogen or C_{1-2}alkyl;

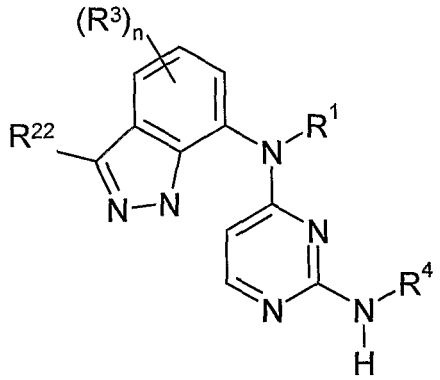
R^{22} is as defined in claim 5 or claim 6;

R^3 is as defined in claim 1 or claim 9;

n is as defined in claim 1 or claim 10, and

R^4 is as defined in any one of claims 1, 11 or 12.

14. A compound according to claim 1, wherein said compound has the general structural formula (IE) shown below



(IE)

wherein R^1 is as defined in any one of claims 1, 7, 8 or 13;

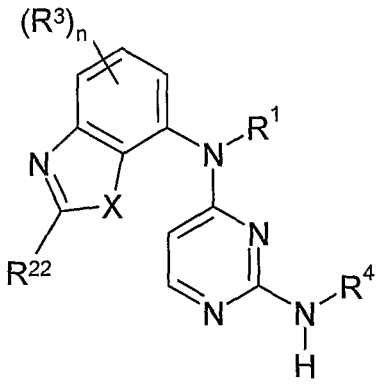
R^{22} is as defined in claim 5 or claim 6;

R^3 is as defined in claim 1 or claim 9;

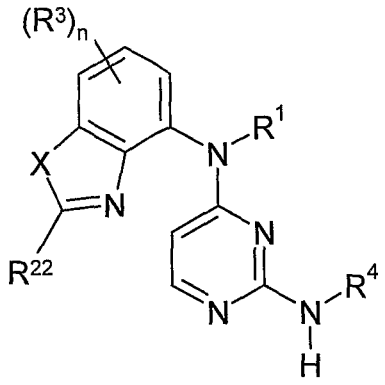
n is as defined in claim 1 or claim 10, and

R^4 is as defined in any one of claims 1, 11 or 12.

15. A compound according to claim 1, wherein said compound has one of the general structural formulae (IF) or (IG) shown below



(IF)



(IG)

wherein X is S or O;

R^1 is as defined in any one of claims 1, 7, 8 or 13;

R^{22} is as defined in claim 5 or claim 6;

R^3 is as defined in claim 1 or claim 9;

n is as defined in claim 1 or claim 10, and

R^4 is as defined in any one of claims 1, 11 or 12.

16. A compound according to claims 14 or 15, wherein R^1 is hydrogen or a C_{1-2}alkyl group, which is optionally substituted with one or more substituents selected from cyano, $-OR^2$, $-NR^{2a}R^{2b}$, where R^2, R^{2a} and R^{2b} are selected from hydrogen or C_{1-2}alkyl.

17. A compound according to any one of claims 13 to 15, wherein R^1 is a C_{1-2}alkyl group, which is optionally substituted with one or more substituents selected from cyano, $-OR^2$, $-NR^{2a}R^{2b}$, where R^2, R^{2a} and R^{2b} are selected from hydrogen or C_{1-2}alkyl.

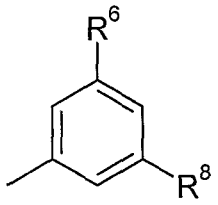
18. A compound according to any one of claims 13 to 15, wherein R^1 is methyl.

19. A compound according to any one of claims 13 to 18, wherein n is 0.

20. A compound according to any one of claims 13 to 19, wherein R^{22} is hydrogen, halo, or C_{1-2}alkyl.

21. A compound according to any one of claims 13 to 20, wherein R^4 is as defined in claim 12.

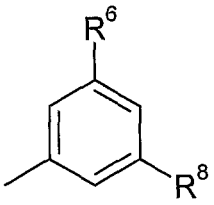
22. A compound according to any one of claims 13 to 20, wherein R^4 is a group of sub-formula (iiib)



(iiib)

wherein both R^6 and R^8 are a 5 or 6-membered nitrogen linked heterocyclylic rings.

23. A compound according to any one of claims 13 to 20, wherein R^4 is a group of sub-formula (iiib)

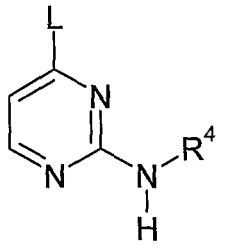


(iiib)

wherein both R^6 and R^8 are morpholin-4-yl.

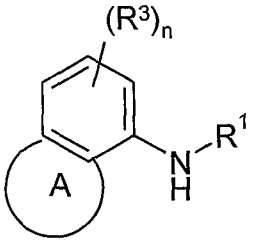
24. A pharmaceutical composition comprising a compound according to any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier or diluent.

25. A process for preparing a compound of formula (I) by reacting a compound of formula (II):



(II)

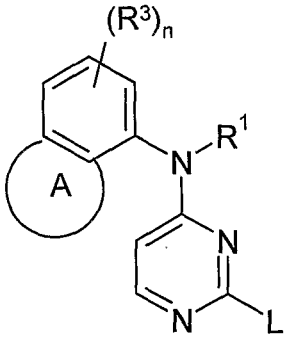
where R^4 is as defined in claim 1 provided that any functional groups are optionally protected, and L is a leaving group, with a compound of formula (III)



(III)

where A, R^1, R^3 and n are as defined in claim 1, provided that any functional groups are optionally protected; or

by reaction a compound of formula (VII)



(VII)

where A, R^3 R^1 and n are as defined in claim 1 provided that any functional groups are optionally protected and L is a leaving group as defined in relation to formula (II), with a compound of formula (VI) as defined above;

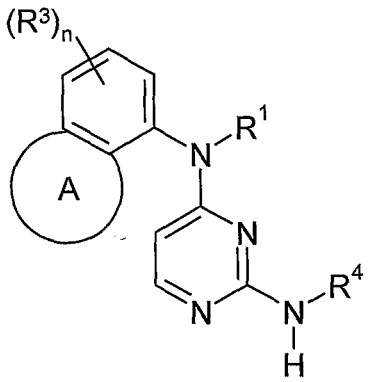
and thereafter if desired or necessary carrying out one or more of the following steps:

(i) removing any protecting groups, or

(ii) converting a compound of formula (I) obtained into a different compound of formula (I);

(iii) forming a salt.

26. The use of a compound of formula (IH)



(IH)

where **R**[1] is selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, or C_{2-6}alkynyl, wherein the alkyl, alkenyl and alkynyl groups are optionally substituted by one or more substituent groups selected from cyano, nitro, $-OR^2$, $-NR^{2a}R^{2b}$, $-C(O)NR^{2a}R^{2b}$, or $-N(R^{2a})C(O)R^2$, halo or haloC_{1-4}alkyl, where R^2, R^{2a} and R^{2b} are selected from hydrogen or C_{1-6}alkyl such as methyl, or R^{2a} and R^{2b} together with the nitrogen atom to which they are attached may form a 5 or 6-membered heterocyclic ring, which optionally contains an additional heteroatom selected from N, O or S;

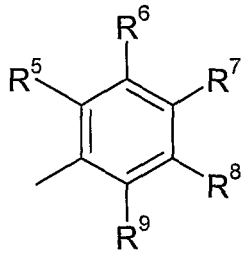
ring **A** is fused 5 or 6-membered carbocyclic or heterocyclic ring, which is saturated or unsaturated, and is optionally substituted on any available carbon atom by one or more substituent groups selected from halo, cyano, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, $-S(O)_z-C_{1-6}$alkyl (where z is 0, 1 or 2), or $-NR^aR^b$ (where R^a and R^b are each independently selected from hydrogen, C_{1-4}alkyl, or C_{1-4}alkylcarbonyl), and where any nitrogen atoms in the ring are optionally substituted by a C_{1-6}alkyl or C_{1-6}alkylcarbonyl;
n is 0, 1, 2 or 3

and each group **R**[3] is independently selected from halo, trifluoromethyl, cyano, nitro or a group of sub-formula (i) :

$$-X^1-R^{11} \qquad (i)$$

where $\mathbf{X^1}$ is selected from a direct bond or O, S, SO, SO_2, OSO_2, NR^{13}, CO, $CH(OR^{13})$, $CONR^{13}$, $N(R^{13})CO$, $SO_2N(R^{13})$, $N(R^{13})SO_2$, $C(R^{13})_2O$, $C(R^{13})_2S$, $C(R^{13})_2N(R^{13})$ and $N(R^{13})C(R^{13})_2$, wherein $\mathbf{R^{13}}$ is hydrogen or C_{1-6}alkyl and $\mathbf{R^{11}}$ is selected from hydrogen, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}cycloalkyl, aryl or heterocyclyl, C_{3-8}cycloalkylC_{1-6} alkyl, arylC_{1-6} alkyl or heterocyclylC_{1-6}alkyl, any of which may be optionally substituted with one or more groups selected from halo, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, C_{1-6}alkoxy, C_{2-6}alkenyoxyl, C_{2-6}alkynyloxy, C_{1-6}alkylthio, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, C_{1-6}alkylamino, di-(C_{1-6}alkyl)amino, C_{1-6}alkoxycarbonyl, N-C_{1-6}alkylcarbamoyl, N, N-di-(C_{1-6}alkyl)carbamoyl, C_{2-6}alkanoyl, C_{2-6}alkanoyloxy, C_{2-6}alkanoylamino, N-C_{1-6}alkyl-C_{2-6}alkanoylamino, C_{3-6}alkenoylamino, N-C_{1-6}alkyl-C_{3-6}alkenoylamino, C_{3-6}alkynoylamino, N-C_{1-6}alkyl- C_{3-6}alkynoylamino, N-C_{1-6}alkylsulphamoyl, N,N-di-(C_{1-6}alkyl)sulphamoyl, C_{1-6}alkanesulphonylamino and N-C_{1-6}alkyl-C_{1-6}alkanesulphonylamino, and any heterocyclyl group within R^{11} optionally bears 1 or 2 oxo or thioxo substituents; and

$\mathbf{R^4}$ is a group of sub-formula (iii)



(iii)

where $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$ and $\mathbf{R^9}$ are each independently selected from:

(i) hydrogen, halo, trifluoromethyl, trifluoromethoxy, cyano, nitro, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl), heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) and wherein any aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl), heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) groups are optionally substituted on any available carbon atoms by halo, hydroxy, cyano, amino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino, and any nitrogen atoms present in a

heterocyclyl group may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl, and where any sulphur atoms may be optionally oxidised to a sulphur oxide;

(ii) a group of sub-formula (iv):

$$-X^2-R^{14} \qquad (iv)$$

where $\mathbf{X^2}$ is selected from O, NR^{16}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{16})$, $CON(R^{16})$, $N(R^{16})CO$, $-N(R^{16})C(O)N(R^{16})-$, $-N(R^{16})C(O)O-$, $SON(R^{16})$, $N(R^{16})SO$, $SO_2N(R^{16})$, $N(R^{16})SO_2$, $C(R^{16})_2O$, $C(R^{16})_2S$ and $N(R^{16})C(R^{16})_2$, where each R^{16} is independently selected from hydrogen or C_{1-6}alkyl,

$\mathbf{R^{14}}$ is hydrogen, C_{1-6} alkyl, trifluoromethyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, or a 4- to 8-membered mono or bicyclic heterocyclyl ring (including 5 or 6 membered heteroaryl rings) or 4- to 8-membered mono or bicyclic heterocyclyl-C_{1-6}alkyl groups (including 5 or 6 membered heteroaryl-C_{1-6}alkyl groups) and wherein any aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl), heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) groups are optionally substituted on any available carbon atoms by oxo, halo, cyano, amino, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino and any nitrogen atoms present in the heterocyclyl moieties may, depending upon valency considerations, be substituted by a group selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl, and where any sulphur atoms may be optionally oxidised to a sulphur oxide;

iii) a group of sub-formula (v):

$$-X^3-R^{15}-Z \qquad (v)$$

where $\mathbf{X^3}$ is a direct bond or is selected from O, NR^{17}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{17})$, $CON(R^{17})$, $N(R^{17})CO$, $-N(R^{17})C(O)N(R^{17})-$, $-N(R^{17})C(O)O-$, $SO_2N(R^{17})$, $N(R^{17})SO_2$, $C(R^{17})_2O$, $C(R^{17})_2S$ and $N(R^{17})C(R^{17})_2$, where each R^{17} is independently selected from hydrogen or C_{1-6}alkyl;

$\mathbf{R^{15}}$ is a C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene, arylene, C_{3-12} carbocyclyl, heterocyclyl (including heteroaryl), any of which may be optionally substituted by one or more groups selected from halo, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, cyano, amino, C_{1-6}alkylamino or di-(C_{1-6}alkyl)amino;

Z is halo, trifluoromethyl, cyano, nitro, aryl, C_{3-12} carbocyclyl or heterocyclyl (including heteroaryl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl and C_{1-6}alkoxy and wherein any heterocyclyl group within Z optionally bears 1 or 2 oxo substituents,

or Z is a group of sub-formula (vi)

$$-X^4-R^{18} \qquad \text{(vi)}$$

where $\mathbf{X^4}$ is selected from O, NR^{19}, S, SO, SO_2, OSO_2, CO, C(O)O, OC(O), $CH(OR^{19})$, $CON(R^{19})$, $N(R^{19})CO$, $SO_2N(R^{19})$, $-N(R^{19})C(O)N(R^{19})-$, $-N(R^{19})C(O)O-$ $N(R^{19})SO_2$, $C(R^{19})_2O$, $C(R^{19})_2S$ and $N(R^{19})C(R^{19})_2$, where each R^{19} is independently selected from hydrogen or C_{1-6}alkyl; and R^{18} is selected from hydrogen, C_{1-6} alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, aryl, C_{3-12} carbocyclyl, aryl-C_{1-6}alkyl, heterocyclyl (including heteroaryl) or heterocyclyl-C_{1-6}alkyl (including heteroaryl-C_{1-6}alkyl) which optionally bears 1 or 2 substituents, which may be the same or different, selected from halo, C_{1-6}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl and C_{1-6}alkoxy, and wherein any heterocyclyl group within R^{18} optionally bears 1 or 2 oxo substituents;

or

(iv) R^5 and R^6, R^6 and R^7, R^7 and R^8 or R^8 and R^9 are joined together to form a fused 5, 6 or 7-membered ring, wherein said ring is unsaturated or partially or fully saturated and is optionally substituted on any available carbon atom by halo, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, amino, N-C_{1-6}alkylamino, or N,N-diC_{1-6}alkylamino, and said ring may contain one or more heteroatoms selected from oxygen, sulphur or nitrogen, where sulphur atoms may be optionally oxidised to a sulphur oxide, where any CH_2 groups may be substituted by a C(O) group, and where nitrogen atoms, depending upon valency considerations, may be substituted by a group R^{21}, where R^{21} is selected from hydrogen, C_{1-6}alkyl or C_{1-6}alkylcarbonyl;

or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for use in the treatment of cancer.

27. The use of a compound according to any one of claims 1 to 23 or 26 in the preparation of a medicament for use in the production of an EphB4 inhibitory effect in a warm-blooded animal such as man.

28. A method for producing an EphB4 inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound according to any one of claims 1 to 23 or 26, or a pharmaceutically acceptable salt thereof.

29. The use of a compound according to any one of claims 1 to 23 or 26, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the production of an anti-angiogenic effect in a warm-blooded animal such as man.

30. A method for producing an anti-angiogenic effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound according to any one of claims 1 to 23 or 26, or a pharmaceutically acceptable salt thereof.

31. A method of treating cancer in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound according to any one of claims 1 to 23 or 26, or a pharmaceutically acceptable salt thereof.

32. A compound according to any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use as a medicament.

33. The use of a compound according to any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for the treatment of cancer.