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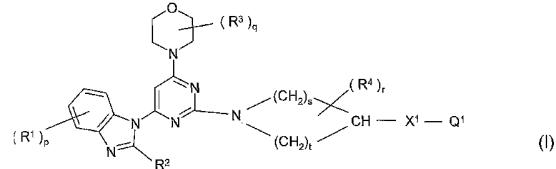
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(54) Title: PYRIMIDINE DERIVATIVES HAVING INHIBITORY ACTIVITY AGAINST PI3K ENZYME



(57) Abstract: The invention concerns pyrimidine derivatives of Formula (I) wherein each of p, R¹, R², q, R³, r, R⁴, s, t, X¹ and Q¹ have any of the meanings defined in the description; processes for their preparation, pharmaceutical compositions containing them and their use in a method for producing an anti-proliferative effect in a warm blooded animal such as man.

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**PYRIMIDINE DERIVATIVES HAVING INHIBITORY ACTIVITY
AGAINST PI3 K ENZYMES**

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

Many of the current treatment regimes for cell proliferation diseases such as cancer and psoriasis 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 anti-tumour agents which act by 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, that is 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-Src} tyrosine kinase (otherwise known as v-Src), and the corresponding tyrosine kinases in normal cells, for example pp60^{c-Src} tyrosine kinase (otherwise known as c-Src).

Receptor tyrosine kinases are important in the transmission of biochemical signals which initiate cell replication. 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) based on families of

growth factors which bind to different receptor tyrosine kinases. The classification includes Class I receptor tyrosine kinases comprising the EGF family of receptor tyrosine kinases such as the EGF, TGF α , Neu and erbB receptors.

It is also known that certain tyrosine kinases belong to the class of non-receptor tyrosine 5 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. Various classes of non-receptor tyrosine kinases are known including the Src family such as the Src, Lyn, Fyn and Yes tyrosine kinases.

It is also known that certain kinases belong to the class of serine/threonine kinases which 10 are located intracellularly and downstream of tyrosine kinase activation and are involved in the transmission of biochemical signals such as those that influence tumour cell growth. Such serine/threonine signalling pathways include the Raf-MEK-ERK cascade and those downstream of the lipid kinase known as PI3K such as PDK-1, AKT and mTOR (Blume-Jensen and Hunter, Nature, 2001, 411, 355).

15 It is also known that certain kinases that belong to the class of lipid kinases are located intracellularly and are also involved in the transmission of biochemical signals such as those that influence tumour cell growth and invasiveness. Various classes of lipid kinases are known including the phosphoinositide 3-kinase (abbreviated hereinafter to PI3K) family that is alternatively known as the phosphatidylinositol-3-kinase family.

20 It is now well understood that deregulation of oncogenes and tumour-suppressor genes contributes to the formation of malignant tumours, for example by way of increased cell proliferation or increased cell survival. It is also now known that signalling pathways mediated by the PI3K family have a central role in a number of cell processes including proliferation and survival, and deregulation of these pathways is a causative factor in a wide 25 spectrum of human cancers and other diseases (Katso *et al.*, Annual Rev. Cell Dev. Biol., 2001, 17: 615-617 and Foster *et al.*, J. Cell Science, 2003, 116: 3037-3040).

30 The PI3K family of lipid kinases is a group of enzymes that phosphorylate the 3-position of the inositol ring of phosphatidylinositol (abbreviated hereinafter to PI). Three major groups of PI3K enzymes are known which are classified according to their physiological substrate specificity (Vanhaesebroeck *et al.*, Trends in Biol. Sci., 1997, 22, 267). Class III PI3K enzymes phosphorylate PI alone. In contrast, Class II PI3K enzymes phosphorylate both PI and PI 4-phosphate [abbreviated hereinafter to PI(4)P]. Class I PI3K enzymes

phosphorylate PI, PI(4)P and PI 4,5-bisphosphate [abbreviated hereinafter to PI(4,5)P₂], although only PI(4,5)P₂ is believed to be the physiological cellular substrate. Phosphorylation of PI(4,5)P₂ produces the lipid second messenger PI 3,4,5-triphosphate [abbreviated hereinafter to PI(3,4,5)P₃]. More distantly related members of this superfamily are Class IV 5 kinases such as mTOR and DNA-dependent kinase that phosphorylate serine/threonine residues within protein substrates. The most studied and understood of these lipid kinases are the Class I PI3K enzymes.

Class I PI3K is a heterodimer consisting of a p110 catalytic subunit and a regulatory subunit, and the family is further divided into Class Ia and Class Ib enzymes on the basis of 10 regulatory partners and mechanism of regulation. Class Ia enzymes consist of three distinct catalytic subunits (p110 α , p110 β and p110 δ) that dimerise with five distinct regulatory subunits (p85 α , p55 α , p50 α , p85 β and p55 γ), with all catalytic subunits being able to interact with all regulatory subunits to form a variety of heterodimers. Class Ia PI3K are generally activated in response to growth factor-stimulation of receptor tyrosine kinases, *via* interaction 15 of the regulatory subunit SH2 domains with specific phospho-tyrosine residues of the activated receptor or adaptor proteins such as IRS-1. Both p110 α and p110 β are constitutively expressed in all cell types, whereas p110 δ expression is more restricted to leukocyte populations and some epithelial cells. In contrast, the single Class Ib enzyme consists of a p110 γ catalytic subunit that interacts with a p101 regulatory subunit. Furthermore, the 20 Class Ib enzyme is activated in response to G-protein coupled receptor (GPCR) systems and its expression appears to be limited to leucocytes.

There is now considerable evidence indicating that Class Ia PI3K enzymes contribute to tumourigenesis in a wide variety of human cancers, either directly or indirectly (Vivanco and Sawyers, *Nature Reviews Cancer*, 2002, 2, 489-501). For example, the p110 α subunit is 25 amplified in some tumours such as those of the ovary (Shayesteh *et al.*, *Nature Genetics*, 1999, 21: 99-102) and cervix (Ma *et al.*, *Oncogene*, 2000, 19: 2739-2744). More recently, activating mutations within the catalytic site of p110 α have been associated with various other tumours such as those of the colorectal region and of the breast and lung (Samuels *et al.*, *Science*, 2004, 304, 554). Tumour-related mutations in p85 α have also been identified in cancers such as 30 those of the ovary and colon (Philp *et al.*, *Cancer Research*, 2001, 61, 7426-7429). In addition to direct effects, it is believed that activation of Class Ia PI3K contributes to tumourigenic events that occur upstream in signalling pathways, for example by way of ligand-dependent or

ligand-independent activation of receptor tyrosine kinases, GPCR systems or integrins (Vara *et al.*, Cancer Treatment Reviews, 2004, 30, 193-204). Examples of such upstream signalling pathways include over-expression of the receptor tyrosine kinase Erb2 in a variety of tumours leading to activation of PI3K-mediated pathways (Harari *et al.*, Oncogene, 2000, 19, 6102-6114) and over-expression of the oncogene Ras (Kauffmann-Zeh *et al.*, Nature, 1997, 385, 544-548). In addition, Class Ia PI3Ks may contribute indirectly to tumourigenesis caused by various downstream signalling events. For example, loss of the effect of the PTEN tumour-suppressor phosphatase that catalyses conversion of PI(3,4,5)P3 back to PI(4,5)P2 is associated with a very broad range of tumours *via* deregulation of PI3K-mediated production of PI(3,4,5)P3 (Simpson and Parsons, Exp. Cell Res., 2001, 264, 29-41). Furthermore, augmentation of the effects of other PI3K-mediated signalling events is believed to contribute to a variety of cancers, for example by activation of Akt (Nicholson and Anderson, Cellular Signalling, 2002, 14, 381-395).

In addition to a role in mediating proliferative and survival signalling in tumour cells, there is also good evidence that Class Ia PI3K enzymes will also contribute to tumourigenesis *via* its function in tumour-associated stromal cells. For example, PI3K signalling is known to play an important role in mediating angiogenic events in endothelial cells in response to pro-angiogenic factors such as VEGF (Abid *et al.*, Arterioscler. Thromb. Vasc. Biol., 2004, 24, 294-300). As Class I PI3K enzymes are also involved in motility and migration (Sawyer, Expert Opinion Investig. Drugs, 2004, 13, 1-19), PI3K inhibitors should provide therapeutic benefit *via* inhibition of tumour cell invasion and metastasis.

In addition, Class I PI3K enzymes play an important role in the regulation of immune cells with PI3K activity contributing to pro-tumourigenic effects of inflammatory cells (Coussens and Werb, Nature, 2002, 420, 860-867).

These findings suggest that pharmacological inhibitors of Class I PI3K enzymes should be of therapeutic value for treatment of the various forms of the disease of cancer comprising solid tumours such as carcinomas and sarcomas and the leukaemias and lymphoid malignancies. In particular, inhibitors of Class I PI3K enzymes should be of therapeutic value for treatment of, for example, cancer of the breast, colorectum, lung (including small cell lung cancer, non-small cell lung cancer and bronchioalveolar cancer) and prostate, and of cancer of the bile duct, bone, bladder, head and neck, kidney, liver, gastrointestinal tissue, oesophagus,

ovary, pancreas, skin, testes, thyroid, uterus, cervix and vulva, and of leukaemias (including ALL and CML), multiple myeloma and lymphomas.

Generally, investigators have explored the physiological and pathological roles of the PI3K enzyme family using the PI3K inhibitors LY294002 and wortmannin. Although use of those compounds may suggest a role for PI3K in a cellular event, they are not sufficiently selective within the PI3K family to allow dissection of the individual roles of the family members. For this reason, more potent and selective pharmaceutical PI3K inhibitors would be useful to allow a more complete understanding of PI3K function and to provide useful therapeutic agents.

In addition to tumourigenesis, there is evidence that Class I PI3K enzymes play a role in other diseases (Wymann *et al.*, Trends in Pharmacological Science, 2003, 24, 366-376). Both Class Ia PI3K enzymes and the single Class Ib enzyme have important roles in cells of the immune system (Koyasu, Nature Immunology, 2003, 4, 313-319) and thus they are therapeutic targets for inflammatory and allergic indications. Inhibition of PI3K is also useful to treat cardiovascular disease *via* anti-inflammatory effects or directly by affecting cardiac myocytes (Prasad *et al.*, Trends in Cardiovascular Medicine, 2003, 13, 206-212). Thus inhibitors of Class I PI3K enzymes are expected to be of value in the prevention and treatment of a wide variety of diseases in addition to cancer.

We have now found that surprisingly certain pyrimidine derivatives possess potent anti-tumour activity, being useful in inhibiting the uncontrolled cellular proliferation which arises from malignant disease. Without wishing to imply that the compounds disclosed in the present invention possess pharmacological activity only by virtue of an effect on a single biological process, it is believed that the compounds provide an anti-tumour effect by way of inhibition of Class I PI3K enzymes, particularly by way of inhibition of the Class Ia PI3K enzymes and/or the Class Ib PI3K enzyme, more particularly by way of inhibition of the Class Ia PI3K enzymes.

The compounds of the present invention are also useful in inhibiting the uncontrolled cellular proliferation which arises from various non-malignant diseases such as inflammatory diseases (for example rheumatoid arthritis and inflammatory bowel disease), fibrotic diseases (for example hepatic cirrhosis and lung fibrosis), glomerulonephritis, multiple sclerosis, psoriasis, benign prostatic hypertrophy (BPH), hypersensitivity reactions of the skin, blood

vessel diseases (for example atherosclerosis and restenosis), allergic asthma, insulin-dependent diabetes, diabetic retinopathy and diabetic nephropathy.

Generally, the compounds of the present invention possess potent inhibitory activity against Class I PI3K enzymes, particularly against Class Ia PI3K enzymes, whilst possessing 5 less potent inhibitory activity against tyrosine kinase enzymes such as the receptor tyrosine kinases, for example EGF receptor tyrosine kinase and/or VEGF receptor tyrosine kinase, or against non-receptor tyrosine kinases such as Src. Furthermore, certain compounds of the present invention, possess substantially better potency against Class I PI3K enzymes, particularly against Class Ia PI3K enzymes, than against EGF receptor tyrosine kinase or 10 VEGF receptor tyrosine kinase or Src non-receptor tyrosine kinase. Such compounds possess sufficient potency against Class I PI3K enzymes that they may be used in an amount sufficient to inhibit Class I PI3K enzymes, particularly to inhibit Class Ia PI3K enzymes, whilst demonstrating little activity against EGF receptor tyrosine kinase or VEGF receptor tyrosine kinase or Src non-receptor tyrosine kinase.

15 It has been noted that at least some of the compounds of the present invention also possess potent inhibitory activity against the Class IV kinase mTOR.

The mammalian target of the macrolide antibiotic Rapamycin (sirolimus) is the enzyme mTOR that belongs to the phosphatidylinositol (PI) kinase-related kinase (PIKK) family of protein kinases, which includes ATM, ATR, DNA-PK and hSMG-1. mTOR, like other PIKK 20 family members, does not possess detectable lipid kinase activity, but instead functions as a serine/threonine kinase. Much of the knowledge of mTOR signalling is based upon the use of Rapamycin. Rapamycin first binds to the 12 kDa immunophilin FK506-binding protein (FKBP12) and this complex inhibits mTOR signalling (Tee and Blenis, Seminars in Cell and Developmental Biology, 2005, 16, 29-37). mTOR protein consists of a catalytic kinase 25 domain, an FKBP12-Rapamycin binding (FRB) domain, a putative repressor domain near the C-terminus and up to 20 tandemly-repeated HEAT motifs at the N-terminus, as well as FRAP-ATM-TRRAP (FAT) and FAT C-terminus domain (Huang and Houghton, Current Opinion in Pharmacology, 2003, 3, 371-377).

mTOR kinase is a key regulator of cell growth and has been shown to regulate a wide 30 range of cellular functions including translation, transcription, mRNA turnover, protein stability, actin cytoskeleton reorganisation and autophagy (Jacinto and Hall, Nature Reviews Molecular and Cell Biology, 2005, 4, 117-126). mTOR kinase integrates signals from growth

5 factors (such as insulin or insulin-like growth factor) and nutrients (such as amino acids and glucose) to regulate cell growth. mTOR kinase is activated by growth factors through the PI3K-Akt pathway. The most well characterised function of mTOR kinase in mammalian cells is regulation of translation through two pathways, namely activation of ribosomal S6K1 to enhance translation of mRNAs that bear a 5'-terminal oligopyrimidine tract (TOP) and suppression of 4E-BP1 to allow CAP-dependent mRNA translation.

10 Generally, investigators have explored the physiological and pathological roles of mTOR using inhibition with Rapamycin and related Rapamycin analogues based on their specificity for mTOR as an intracellular target. However, recent data suggests that Rapamycin displays variable inhibitory actions on mTOR signalling functions and suggest that direct 15 inhibition of the mTOR kinase domain may display substantially broader anti-cancer activities than that achieved by Rapamycin (Edinger *et al.*, Cancer Research, 2003, 63, 8451-8460). For this reason, potent and selective inhibitors of mTOR kinase activity would be useful to allow a more complete understanding of mTOR kinase function and to provide useful therapeutic agents.

15 There is now considerable evidence indicating that the pathways upstream of mTOR are frequently activated in cancer (Vivanco and Sawyers, Nature Reviews Cancer, 2002, 2, 489-501; Bjornsti and Houghton, Nature Reviews Cancer, 2004, 4, 335-348; Inoki *et al.*, Nature Genetics, 2005, 37, 19-24). For example, components of the PI3K pathway that are mutated in 20 different human tumours include activating mutations of growth factor receptors and the amplification and/or overexpression of PI3K and Akt.

25 In addition there is evidence that endothelial cell proliferation may also be dependent upon mTOR signalling. Endothelial cell proliferation is stimulated by vascular endothelial cell growth factor (VEGF) activation of the PI3K-Akt-mTOR signalling pathway (Dancey, Expert Opinion on Investigational Drugs, 2005, 14, 313-328). Moreover, mTOR kinase signalling is believed to partially control VEGF synthesis through effects on the expression of hypoxia-inducible factor-1 α (HIF-1 α) (Hudson *et al.*, Molecular and Cellular Biology, 2002, 22, 7004-7014). Therefore, tumour angiogenesis may depend on mTOR kinase signalling in two ways, through hypoxia-induced synthesis of VEGF by tumour and stromal cells, and through VEGF 30 stimulation of endothelial proliferation and survival through PI3K-Akt-mTOR signalling.

These findings suggest that pharmacological inhibitors of mTOR kinase should be of therapeutic value for treatment of the various forms of the disease of cancer comprising solid tumours such as carcinomas and sarcomas and the leukaemias and lymphoid malignancies.

In addition to tumourigenesis, there is evidence that mTOR kinase plays a role in an array of hamartoma syndromes. Recent studies have shown that the tumour suppressor proteins such as TSC1, TSC2, PTEN and LKB1 tightly control mTOR kinase signalling. Loss of these tumour suppressor proteins leads to a range of hamartoma conditions as a result of elevated mTOR kinase signalling (Tee and Blenis, Seminars in Cell and Developmental Biology, 2005, 16, 29-37). Syndromes with an established molecular link to dysregulation of mTOR kinase include Peutz-Jeghers syndrome (PJS), Cowden disease, Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus syndrome, Lhermitte-Duclos disease and TSC (Inoki *et al.*, Nature Genetics, 2005, 37, 19-24). Patients with these syndromes characteristically develop benign hamartomatous tumours in multiple organs.

Recent studies have revealed a role for mTOR kinase in other diseases (Easton & Houghton, Expert Opinion on Therapeutic Targets, 2004, 8, 551-564). Rapamycin has been demonstrated to be a potent immunosuppressant by inhibiting antigen-induced proliferation of T cells, B cells and antibody production (Sehgal, Transplantation Proceedings, 2003, 35, 7S-14S) and thus mTOR kinase inhibitors may also be useful immunosuppressives. Inhibition of the kinase activity of mTOR may also be useful in the prevention of restenosis, that is the control of undesired proliferation of normal cells in the vasculature in response to the introduction of stents in the treatment of vasculature disease (Morice *et al.*, New England Journal of Medicine, 2002, 346, 1773-1780). Furthermore, the Rapamycin analogue, everolimus, can reduce the severity and incidence of cardiac allograft vasculopathy (Eisen *et al.*, New England Journal of Medicine, 2003, 349, 847-858). Elevated mTOR kinase activity has been associated with cardiac hypertrophy, which is of clinical importance as a major risk factor for heart failure and is a consequence of increased cellular size of cardiomyocytes (Tee & Blenis, Seminars in Cell and Developmental Biology, 2005, 16, 29-37). Thus mTOR kinase inhibitors are expected to be of value in the prevention and treatment of a wide variety of diseases in addition to cancer.

It is disclosed in European Patent Application No. 1020462 that certain triazine and pyrimidine derivatives that are substituted with both a 1-benzimidazolyl group and a morpholino group possess anti-tumour activity and are useful in the treatment of cancer.

There is the disclosure of certain triazines that are substituted by each of a benzimidazol-1-yl group, a morpholino group and a piperidino group, such as 2-benzimidazol-1-yl-4-morpholino-6-piperidino-1,3,5-triazine (compound 15) and 2-benzimidazol-1-yl-4-(4-hydroxypiperidino)-6-morpholino-1,3,5-triazine (compound 5). There is no specific
5 disclosure of any pyrimidines that are substituted by each of a benzimidazol-1-yl group, a morpholino group and a piperidino group.

It is disclosed in International Patent Application WO 00/043385 that certain further triazine and pyrimidine derivatives that are substituted with both a 1-benzimidazolyl group and a morpholino group possess anti-tumour activity and are useful in the treatment of cancer.

10 There is the disclosure of certain triazines that are substituted by each of a benzimidazol-1-yl group, a morpholino group and a pyrrolidinyl group, such as 2-benzimidazol-1-yl-4-morpholino-6-(2-hydroxymethylpyrrolidin-1-yl)-1,3,5-triazine. There is no specific disclosure of any pyrimidines that are substituted by each of a benzimidazol-1-yl group, a morpholino group and a pyrrolidinyl group.

15 It is disclosed in European Patent Application No. 1389617 that certain further triazine and pyrimidine derivatives that are substituted with both a 1-benzimidazolyl group and a morpholino group possess anti-tumour activity and are useful in the treatment of cancer.
There is the disclosure of certain pyrimidines substituted by each of a substituted
benzimidazol-1-yl group, a substituted morpholino group and a pyrrolidinyl or piperidino
20 group, namely 4-(*cis*-2,3-dimethylmorpholino)-2-(2-hydroxymethylbenzimidazol-1-yl)-
6-(2-hydroxymethylpyrrolidin-1-yl)pyrimidine (compound 12) and
4-(*cis*-2,3-dimethylmorpholino)-2-(2-hydroxymethylbenzimidazol-1-yl)-
6-piperidinopyrimidine (compound 11).

25 It is disclosed in European Patent Application No. 1557415 that certain further triazine and pyrimidine derivatives that are substituted with both a 1-benzimidazolyl group and a morpholino group possess anti-tumour activity and are useful in the treatment of cancer.
There is the disclosure of a pyrimidine substituted by each of a substituted benzimidazol-1-yl group, a substituted morpholino group and a pyrrolidinyl group, namely
30 2-(2-difluoromethyl-4-hydroxybenzimidazol-1-yl)-4-(2-hydroxymethylpyrrolidin-1-yl)-
6-morpholinopyrimidine (compound 1).

It is disclosed in International Patent Application WO 2005/095389 that certain further triazine and pyrimidine derivatives that are substituted with both a 1-benzimidazolyl group and

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a morpholino group possess anti-tumour activity and are useful in the treatment of cancer. The scope of disclosure does not embrace any triazines or pyrimidines that are substituted by each of a benzimidazol-1-yl group, a morpholino group and a pyrrolidinyl or piperidinyl group.

It is disclosed in International Patent Application WO 2006/005914 that certain 5 pyrimidine derivatives possess PI3K enzyme inhibitory activity and are useful in the treatment of cancer. The disclosure focuses on 2,4-diaryl-6-morpholinopyrimidines. The scope of disclosure does not embrace benzimidazolyl substituted pyrimidines.

It is disclosed in International Patent Application WO 2006/005918 that certain 10 pyrimidine derivatives possess PI3K enzyme inhibitory activity and are useful in the treatment of cancer. The disclosure focuses on 2,4-diaryl-6-morpholinopyrimidines. The scope of disclosure does not embrace benzimidazolyl substituted pyrimidines.

It is disclosed in International Patent Application WO 2006/005915 that certain 15 pyrimidine derivatives possess PI3K enzyme inhibitory activity and are useful in the treatment of cancer. The disclosure focuses on 4-heteroaryl-6-morpholinopyrimidines and there is also the disclosure of certain 2-heteroaryl-6-morpholinopyrimidines. There is the disclosure of a 2-(1*H*-benzimidazol-4-yl)-6-morpholinopyrimidine. There is no specific disclosure of any 2-benzimidazol-1-yl substituted pyrimidines.

It is disclosed in International Patent Application WO 2004/048365 that certain 20 pyrimidine derivatives possess PI3K enzyme inhibitory activity and are useful in the treatment of cancer. The disclosure focuses on arylamino- and heteroaryl amino-substituted pyrimidines. The scope of disclosure does not embrace 4-heteroaryl substituted pyrimidines. There is the disclosure of compounds such as :-

25 6-(3-hydroxyphenyl)-2-morpholino-4-[4-(4-nitrophenyl)piperazin-1-yl]pyrimidine (no. 82);
6-(3-hydroxyphenyl)-2-morpholino-4-(4-pyridin-2-ylpiperazin-1-yl)pyrimidine (no. 85);
4-(4-acetyl piperazin-1-yl)-6-(3-hydroxyphenyl)-2-morpholinopyrimidine (no. 86) and
6-(3-hydroxyphenyl)-2-morpholino-4-[4-(2-dimethylaminoethyl)piperazin-1-yl]pyrimidine
(no. 128).

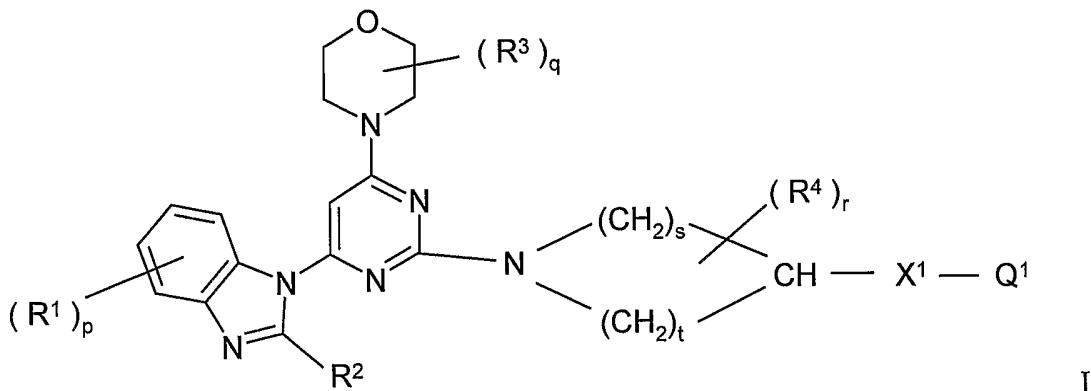
30 It is disclosed in European Patent Application 1277738 that a variety of structures possess PI3K enzyme inhibitory activity and are useful in the treatment of cancer. The disclosure includes mention of 4-morpholino-substituted bicyclic heteroaryl compounds such as quinazoline and pyrido[3,2-*d*]pyrimidine derivatives and 4-morpholino-substituted tricyclic

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heteroaryl compounds such as compounds described as pyrido[3',2':4,5]furo[3,2-d]pyrimidine derivatives. The scope of disclosure does not embrace monocyclic pyrimidine derivatives.

It is disclosed in International Patent Application WO 2005/007648 that certain pyridine, pyrimidine and triazine derivatives that are substituted with a 4-arylpiperazin-1-yl group or with a 4-heteroarylpiperazin-1-yl group are useful in the treatment of acute or chronic pain.
 5 For example, there is the disclosure of many 2-piperazin-1-ylpyrimidine compounds such as :-
 4-(2-fluorophenyl)-6-morpholino-2-(4-pyridin-2-ylpiperazin-1-yl)pyrimidine (no. 87);
 and also of 2-aryl-4-piperazin-1-ylpyrimidine compounds such as :-
 2-(3-chlorophenyl)-6-morpholino-4-[4-(3-trifluoromethylpyridin-2-yl)piperazin-1-
 10 yl]pyrimidine and
 4-[4-(3-chloropyridin-2-yl)-2-methylpiperazin-1-yl]-2-(3,4-difluorophenyl)-
 6-morpholinopyrimidine (no. 92).

According to one aspect of the invention there is provided a pyrimidine derivative of the Formula I



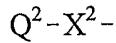
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wherein p is 0, 1, 2 or 3;

each R¹ group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyll, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, 25 N-(1-6C)alkyl-(3-6C)alkynoylamino, N'-(1-6C)alkylureido, N,N'-di-[(1-6C)alkyl]ureido,

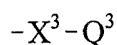
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N-(1-6C)alkylureido, *N,N'*-di-[(1-6C)alkyl]ureido, *N,N',N'*-tri-[(1-6C)alkyl]ureido,
N-(1-6C)alkylsulphamoyl, *N,N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and
N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



5 wherein X^2 is a direct bond or is selected from O, S, SO, SO₂, N(R⁵), CO, CH(OR⁵), CON(R⁵),
 N(R⁵)CO, N(R⁵)CON(R⁵), SO₂N(R⁵), N(R⁵)SO₂, OC(R⁵)₂, SC(R⁵)₂ and N(R⁵)C(R⁵)₂, wherein
 R⁵ is hydrogen or (1-8C)alkyl, and Q² is aryl, aryl-(1-6C)alkyl,
 (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, (3-8C)cycloalkenyl,
 (3-8C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocycl or
 10 heterocycl-(1-6C)alkyl, or (R¹)_p is (1-3C)alkylenedioxy,

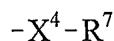
and wherein any CH, CH₂ or CH₃ group within a R¹ substituent optionally bears on each
 said CH, CH₂ or CH₃ group one or more halogeno or (1-8C)alkyl substituents and/or a
 substituent selected from hydroxy, mercapto, amino, cyano, carboxy, carbamoyl, ureido,
 (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino,
 15 di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl,
N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,
N-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylureido, *N'*-(1-6C)alkylureido,
N',N'-di-[(1-6C)alkyl]ureido, *N,N'*-di-[(1-6C)alkyl]ureido, *N,N',N'*-tri-[(1-6C)alkyl]ureido,
 20 *N*-(1-6C)alkylsulphamoyl, *N,N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and
N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



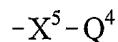
wherein X^3 is a direct bond or is selected from O, S, SO, SO₂, N(R⁶), CO, CH(OR⁶),
 CON(R⁶), N(R⁶)CO, N(R⁶)CON(R⁶), SO₂N(R⁶), N(R⁶)SO₂, C(R⁶)₂O, C(R⁶)₂S and
 C(R⁶)₂N(R⁶), wherein R⁶ is hydrogen or (1-8C)alkyl, and Q³ is aryl, aryl-(1-6C)alkyl,
 25 (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, (3-8C)cycloalkenyl, (3-8C)cycloalkenyl-
 (1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocycl or heterocycl-(1-6C)alkyl,
 and wherein any aryl, (3-8C)cycloalkyl, (3-8C)cycloalkenyl, heteroaryl or heterocycl
 group within a substituent on R¹ optionally bears 1, 2 or 3 substituents, which may be the same
 or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy,
 30 carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy,
 (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl,
 (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl,

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(2-6C)alkanoyl, (2-6C)alkanoyloxy, *N*-(1-6C)alkylcarbamoyl, *N,N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylureido, *N'*-(1-6C)alkylureido, *N,N'*-di-[(1-6C)alkyl]ureido, *N,N'*-di-[(1-6C)alkyl]ureido, *N,N',N'*-tri-[(1-6C)alkyl]ureido, *N*-(1-6C)alkylsulphamoyl, *N,N*-di-[(1-6C)alkyl]sulphamoyl,
5 (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X^4 is a direct bond or is selected from O and N(R^8), wherein R^8 is hydrogen or (1-8C)alkyl, and R^7 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, mercapto-(1-6C)alkyl,
10 (1-6C)alkoxy-(1-6C)alkyl, (1-6C)alkylthio-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl, *N*-(1-6C)alkylureido-(1-6C)alkyl, *N'*-(1-6C)alkylureido-(1-6C)alkyl,
15 *N,N'*-di-[(1-6C)alkyl]ureido-(1-6C)alkyl, *N,N'*-di-[(1-6C)alkyl]ureido-(1-6C)alkyl or *N,N',N'*-tri-[(1-6C)alkyl]ureido-(1-6C)alkyl, or from a group of the formula :



wherein X^5 is a direct bond or is selected from O, CO and N(R^9), wherein R^9 is hydrogen or (1-8C)alkyl, and Q^4 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same
20 or different, selected from halogeno, hydroxy, (1-8C)alkyl and (1-6C)alkoxy,

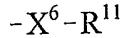
and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo or thioxo substituents,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂,
25 $N(R^{10})$, CO, CH(OR¹⁰), CON(R¹⁰), $N(R^{10})CO$, $N(R^{10})CON(R^{10})$, $SO_2N(R^{10})$, $N(R^{10})SO_2$, CH=CH and C≡C wherein R^{10} is hydrogen or (1-8C)alkyl;

R^2 is fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, hydroxy, amino, formamido, (1-6C)alkoxycarbonylamino, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, hydroxy-(1-6C)alkyl or (1-6C)alkoxy-(1-6C)alkyl;
30 q is 0, 1, 2, 3 or 4;

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each R³ group, which may be the same or different, is (1-8C)alkyl or a group of the formula :



wherein X⁶ is a direct bond or is selected from O and N(R¹²), wherein R¹² is hydrogen or

5 (1-8C)alkyl, and R¹¹ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl or (2-6C)alkanoylamino-(1-6C)alkyl, or two R³ groups together form a methylene, ethylene or trimethylene group;

r is 0, 1, 2, 3 or 4;

10 **each R⁴ group**, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, mercapto, amino, carboxy, carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N'-(1-6C)alkylureido, N',N'-di-[(1-6C)alkyl]ureido, N-(1-6C)alkylureido, N,N'-di-[(1-6C)alkyl]ureido, N,N',N'-tri-[(1-6C)alkyl]ureido, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino,

15 or two R⁴ groups together form a methylene, ethylene or trimethylene group;

s is 1 or 2;

t is 1, 2 or 3;

20 **X¹** is a direct bond or is selected from CO, N(R¹³)CO, CON(R¹³), N(R¹³)CON(R¹³), N(R¹³)COC(R¹³)₂O, N(R¹³)COC(R¹³)₂S, N(R¹³)COC(R¹³)₂N(R¹³) and N(R¹³)COC(R¹³)₂N(R¹³)CO, wherein R¹³ is hydrogen or (1-8C)alkyl; and

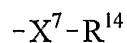
25 **Q¹** is (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, mercapto-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (1-6C)alkylthio-(1-6C)alkyl, (1-6C)alkylsulphanyl-(1-6C)alkyl, (1-6C)alkylsulphonyl-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, N-(1-6C)alkyl-(2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl, N-(1-6C)alkylureido-(1-6C)alkyl, N'-(1-6C)alkylureido-(1-6C)alkyl,

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N',N'-di-[(1-6C)alkyl]ureido-(1-6C)alkyl, N,N'-di-[(1-6C)alkyl]ureido-(1-6C)alkyl,
N,N',N'-tri-[(1-6C)alkyl]ureido-(1-6C)alkyl, (1-6C)alkanesulphonylamino-(1-6C)alkyl or
N-(1-6C)alkyl-(1-6C)alkanesulphonylamino-(1-6C)alkyl,
or Q¹ is aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl,
(3-8C)cycloalkenyl, (3-8C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl,
heterocycl or heterocycl-(1-6C)alkyl,

5 and wherein any CH, CH₂ or CH₃ group within the Q¹ group optionally bears on each
 said CH, CH₂ or CH₃ group one or more halogeno or (1-8C)alkyl substituents and/or a
 substituent selected from hydroxy, mercapto, amino, cyano, carboxy, carbamoyl, ureido,
 10 (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino,
 di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl,
 N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,
 N-(1-6C)alkyl-(2-6C)alkanoylamino, N'-(1-6C)alkylureido, N',N'-di-[(1-6C)alkyl]ureido,
 N-(1-6C)alkylureido, N,N'-di-[(1-6C)alkyl]ureido, N,N',N'-tri-[(1-6C)alkyl]ureido,
 15 N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and
 N-(1-6C)alkyl-(1-6C)alkanesulphonylamino,

15 and wherein any aryl, (3-8C)cycloalkyl, (3-8C)cycloalkenyl, heteroaryl or heterocycl
 group within the Q¹ group optionally bears 1, 2 or 3 substituents, which may be the same or
 different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy,
 20 carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy,
 (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl,
 (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl,
 (2-6C)alkanoyl, (2-6C)alkanoyloxy, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl,
 (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N'-(1-6C)alkylureido,
 25 N',N'-di-[(1-6C)alkyl]ureido, N-(1-6C)alkylureido, N,N'-di-[(1-6C)alkyl]ureido,
 N,N',N'-tri-[(1-6C)alkyl]ureido, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl,
 (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a
 group of the formula :



30 wherein X⁷ is a direct bond or is selected from O and N(R¹⁵), wherein R¹⁵ is hydrogen or
 (1-8C)alkyl, and R¹⁴ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl,

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cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or
di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :

$-X^8-Q^5$

wherein X^8 is a direct bond or is selected from O, CO and N(R^{17}), wherein R^{17} is hydrogen or
5 (1-8C)alkyl, and Q^5 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl
or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same
or different, selected from halogeno, hydroxy, (1-8C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within the Q^1 group optionally bears 1 or 2 oxo or
thioxo substituents,

10 and wherein adjacent carbon atoms in any (2-6C)alkylene chain within the Q^1 group are
optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂,
 $N(R^{16})$, $N(R^{16})CO$, $CON(R^{16})$, $N(R^{16})CON(R^{16})$, CO, CH(OR¹⁶), $N(R^{16})SO_2$, $SO_2N(R^{16})$,
 $CH=CH$ and $C\equiv C$ wherein R^{16} is hydrogen or (1-8C)alkyl;

15 and wherein the 5-position on the pyrimidine ring may optionally bear a (1-8C)alkyl
group;
or a pharmaceutically-acceptable salt thereof.

According to another aspect of the invention there is provided a pyrimidine derivative of
the Formula I above wherein

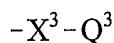
p is 0, 1, 2 or 3;

20 each R^1 group, which may be the same or different, is selected from halogeno,
trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy,
carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy,
(2-6C)alkenyloxy, (2-6C)alkynyoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyll,
(1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl,
25 N -(1-6C)alkylcarbamoyl, N,N -di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl,
(2-6C)alkanoyloxy, (2-6C)alkanoylamino, N -(1-6C)alkyl-(2-6C)alkanoylamino,
(3-6C)alkenoylamino, N -(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino,
 N -(1-6C)alkyl-(3-6C)alkynoylamino, N' -(1-6C)alkylureido, N',N' -di-[(1-6C)alkyl]ureido,
 N -(1-6C)alkylureido, N,N' -di-[(1-6C)alkyl]ureido, N,N',N' -tri-[(1-6C)alkyl]ureido,
30 N -(1-6C)alkylsulphamoyl, N,N -di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and
 N -(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

Q^2-X^2-

wherein X² is a direct bond or is selected from O, S, SO, SO₂, N(R⁵), CO, CH(OR⁵), CON(R⁵), N(R⁵)CO, N(R⁵)CON(R⁵), SO₂N(R⁵), N(R⁵)SO₂, OC(R⁵)₂, SC(R⁵)₂ and N(R⁵)C(R⁵)₂, wherein R⁵ is hydrogen or (1-8C)alkyl, and Q² is aryl, aryl-(1-6C)alkyl,
 (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, (3-8C)cycloalkenyl,
 5 (3-8C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or (R¹)_p is (1-3C)alkylenedioxy,

and wherein any CH, CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH, CH₂ or CH₃ group one or more halogeno or (1-8C)alkyl substituents and/or a substituent selected from hydroxy, mercapto, amino, cyano, carboxy, carbamoyl, ureido, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylureido, N'-(1-6C)alkylureido, N',N'-di-[(1-6C)alkyl]ureido, N,N',N'-tri-[(1-6C)alkyl]ureido, 10 N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X³ is a direct bond or is selected from O, S, SO, SO₂, N(R⁶), CO, CH(OR⁶), CON(R⁶), N(R⁶)CO, N(R⁶)CON(R⁶), SO₂N(R⁶), N(R⁶)SO₂, C(R⁶)₂O, C(R⁶)₂S and C(R⁶)₂N(R⁶), wherein R⁶ is hydrogen or (1-8C)alkyl, and Q³ is aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, (3-8C)cycloalkenyl, (3-8C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any aryl, (3-8C)cycloalkyl, (3-8C)cycloalkenyl, heteroaryl or heterocyclyl group within a substituent on R¹ optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylureido, N'-(1-6C)alkylureido, N',N'-di-[(1-6C)alkyl]ureido, N,N'-di-[(1-6C)alkyl]ureido, 25 N,N',N'-tri-[(1-6C)alkyl]ureido, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl,

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(1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$-X^4-R^7$

wherein X^4 is a direct bond or is selected from O and N(R^8), wherein R^8 is hydrogen or (1-8C)alkyl, and R^7 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, mercapto-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, (1-6C)alkylthio-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl, *N*-(1-6C)alkylureido-(1-6C)alkyl, *N'*-(1-6C)alkylureido-(1-6C)alkyl,

10 N',N' -di-[(1-6C)alkyl]ureido-(1-6C)alkyl, N,N' -di-[(1-6C)alkyl]ureido-(1-6C)alkyl or N,N',N' -tri-[(1-6C)alkyl]ureido-(1-6C)alkyl, or from a group of the formula :

$-X^5-Q^4$

wherein X^5 is a direct bond or is selected from O, CO and N(R^9), wherein R^9 is hydrogen or (1-8C)alkyl, and Q^4 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, hydroxy, (1-8C)alkyl and (1-6C)alkoxy,

15 and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo or thioxo substituents,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent 20 are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R^{10}), CO, CH(OR¹⁰), CON(R^{10}), N(R^{10})CO, N(R^{10})CON(R^{10}), SO₂N(R^{10}), N(R^{10})SO₂, CH=CH and C≡C wherein R^{10} is hydrogen or (1-8C)alkyl;

25 R^2 is fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, hydroxy, amino, formamido, (1-6C)alkoxycarbonylamino, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, hydroxy-(1-6C)alkyl or (1-6C)alkoxy-(1-6C)alkyl;

q is 0, 1, 2, 3 or 4;

each R^3 group, which may be the same or different, is (1-8C)alkyl or a group of the formula :

$-X^6-R^{11}$

30 wherein X^6 is a direct bond or is selected from O and N(R^{12}), wherein R^{12} is hydrogen or (1-8C)alkyl, and R^{11} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl,

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(1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl or (2-6C)alkanoylamino-(1-6C)alkyl,

or two R³ groups together form a methylene, ethylene or trimethylene group;

r is 0, 1, 2, 3 or 4;

5 each R⁴ group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, mercapto, amino, carboxy, carbamoyl, ureido,

(1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio,

(1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino,

(1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl,

10 (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-

(2-6C)alkanoylamino, N'-(1-6C)alkylureido, N',N'-di-[(1-6C)alkyl]ureido,

N-(1-6C)alkylureido, N,N'-di-[(1-6C)alkyl]ureido, N,N',N'-tri-[(1-6C)alkyl]ureido,

15 N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and

N-(1-6C)alkyl-(1-6C)alkanesulphonylamino,

or two R⁴ groups together form a methylene, ethylene or trimethylene group;

s is 1 or 2;

t is 1, 2 or 3;

X¹ is selected from CO, N(R¹³)CO, CON(R¹³), N(R¹³)CON(R¹³), N(R¹³)CO(N(R¹³))₂O, N(R¹³)CO(N(R¹³))₂S, N(R¹³)CO(N(R¹³))₂N(R¹³) and N(R¹³)CO(N(R¹³))₂N(R¹³)CO, wherein R¹³ is hydrogen or (1-8C)alkyl; and

20 Q¹ is (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, halogeno-(1-6C)alkyl,

hydroxy-(1-6C)alkyl, mercapto-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl,

amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl,

(1-6C)alkylthio-(1-6C)alkyl, (1-6C)alkylsulphanyl-(1-6C)alkyl,

25 (1-6C)alkylsulphonyl-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl,

N-(1-6C)alkyl-(2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl,

N-(1-6C)alkylureido-(1-6C)alkyl, N'-(1-6C)alkylureido-(1-6C)alkyl,

N',N'-di-[(1-6C)alkyl]ureido-(1-6C)alkyl, N,N'-di-[(1-6C)alkyl]ureido-(1-6C)alkyl,

N,N',N'-tri-[(1-6C)alkyl]ureido-(1-6C)alkyl, (1-6C)alkanesulphonylamino-(1-6C)alkyl or

30 N-(1-6C)alkyl-(1-6C)alkanesulphonylamino-(1-6C)alkyl,

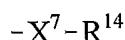
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or Q¹ is aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, (3-8C)cycloalkenyl, (3-8C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

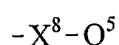
and wherein any CH, CH₂ or CH₃ group within the Q¹ group optionally bears on each

5 said CH, CH₂ or CH₃ group one or more halogeno or (1-8C)alkyl substituents and/or a
substituent selected from hydroxy, mercapto, amino, cyano, carboxy, carbamoyl, ureido,
(1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino,
di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl,
N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,
10 N-(1-6C)alkyl-(2-6C)alkanoylamino, N'-(1-6C)alkylureido, N',N'-di-[(1-6C)alkyl]ureido,
N-(1-6C)alkylureido, N,N'-di-[(1-6C)alkyl]ureido, N,N',N'-tri-[(1-6C)alkyl]ureido,
N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and
N-(1-6C)alkyl-(1-6C)alkanesulphonylamino,

15 and wherein any aryl, (3-8C)cycloalkyl, (3-8C)cycloalkenyl, heteroaryl or heterocyclyl
group within the Q¹ group optionally bears 1, 2 or 3 substituents, which may be the same or
different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy,
carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy,
(2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl,
(1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl,
20 (2-6C)alkanoyl, (2-6C)alkanoyloxy, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl,
(2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N'-(1-6C)alkylureido,
N',N'-di-[(1-6C)alkyl]ureido, N-(1-6C)alkylureido, N,N'-di-[(1-6C)alkyl]ureido,
N,N',N'-tri-[(1-6C)alkyl]ureido, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl,
25 (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a
group of the formula :



wherein X⁷ is a direct bond or is selected from O and N(R¹⁵), wherein R¹⁵ is hydrogen or
(1-8C)alkyl, and R¹⁴ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl,
cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or
30 di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :



wherein X⁸ is a direct bond or is selected from O, CO and N(R¹⁷), wherein R¹⁷ is hydrogen or (1-8C)alkyl, and Q⁵ is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, hydroxy, (1-8C)alkyl and (1-6C)alkoxy,

5 and wherein any heterocyclyl group within the Q¹ group optionally bears 1 or 2 oxo or thioxo substituents,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within the Q¹ group are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R¹⁶), N(R¹⁶)CO, CON(R¹⁶), N(R¹⁶)CON(R¹⁶), CO, CH(OR¹⁶), N(R¹⁶)SO₂, SO₂N(R¹⁶),
10 CH=CH and C≡C wherein R¹⁶ is hydrogen or (1-8C)alkyl;

and wherein the 5-position on the pyrimidine ring may optionally bear a (1-8C)alkyl group;

or a pharmaceutically-acceptable salt thereof.

In this specification the generic term “(1-8C)alkyl” includes both straight-chain and
15 branched-chain alkyl groups such as propyl, isopropyl and *tert*-butyl, and also (3-8C)cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and also (3-6C)cycloalkyl-(1-2C)alkyl groups such as cyclopropylmethyl, 2-cyclopropylethyl, cyclobutylmethyl, 2-cyclobutylethyl, cyclopentylmethyl, 2-cyclopentylethyl, cyclohexylmethyl and 2-cyclohexylethyl. However references to
20 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 and references to individual cycloalkyl groups such as “cyclopentyl” are specific for that 5-membered ring only. An analogous convention applies to other generic terms, for example (1-6C)alkoxy includes (3-6C)cycloalkyloxy groups and
25 (3-5C)cycloalkyl-(1-2C)alkoxy groups, for example methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cyclopropylmethoxy, 2-cyclopropylethoxy, cyclobutylmethoxy, 2-cyclobutylethoxy and cyclopentylmethoxy; (1-6C)alkylamino includes (3-6C)cycloalkylamino groups and (3-5C)cycloalkyl-(1-2C)alkylamino groups, for example methylamino, ethylamino, propylamino,
30 cyclopropylamino, cyclobutylamino, cyclohexylamino, cyclopropylmethylethylamino, 2-cyclopropylethylamino, cyclobutylmethylethylamino, 2-cyclobutylethylamino and cyclopentylmethylethylamino; and di-[(1-6C)alkyl]amino includes di-[(3-6C)cycloalkyl]amino

groups and di-[(3-5C)cycloalkyl-(1-2C)alkyl]amino groups, for example dimethylamino, diethylamino, dipropylamino, *N*-cyclopropyl-*N*-methylamino, *N*-cyclobutyl-*N*-methylamino, *N*-cyclohexyl-*N*-ethylamino, *N*-cyclopropylmethyl-*N*-methylamino, *N*-(2-cyclopropylethyl)-*N*-methylamino and *N*-cyclopentylmethyl-*N*-methylamino.

5 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 10 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.

15 It is to be understood that certain compounds of Formula I defined above may exhibit the phenomenon of tautomerism. In particular, tautomerism may affect the benzimidazolyl group when R² is a hydroxy or amino group or tautomerism may affect heterocyclic groups within the R¹ and Q¹ groups that bear 1 or 2 oxo or thioxo substituents. It is to be understood that the present invention includes in its definition any such tautomeric form, or a mixture thereof, 20 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.

25 It is to be understood that any R¹ group that is present on the phenyl ring portion of the benzimidazolyl group that is located at the 4-position on the pyrimidine ring may be located at any available position on said phenyl ring. When multiple R¹ groups are present, the R¹ groups may be the same or different. Conveniently, no R¹ group is present (p=0) or there is a single R¹ group (p=1). Conveniently, a single R¹ group is located at the 4-, 5- or 6-position on 30 said benzimidazolyl group. Conveniently, a single R¹ group is located at the 4-position on said benzimidazolyl group.

It is further to be understood that any R³ group that may be present on the morpholinyl group that is located at the 6-position on the pyrimidine ring may be located at any available position on said morpholinyl group. Conveniently, when the R³ group is a (1-8C)alkyl group such as a methyl group, up to four such groups are present. Any two such groups may be located at the same ring position on said morpholinyl group. When two R³ groups together form a methylene, ethylene or trimethylene group, a suitable group so formed is, for example,

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a 3-oxa-6-azabicyclo[3.1.1]hept-6-yl, 6-oxa-3-azabicyclo[3.1.1]hept-3-yl, 3-oxa-8-azabicyclo[3.2.1]oct-8-yl or 8-oxa-3-azabicyclo[3.2.1]oct-3-yl group. Conveniently, there is a single R³ group. More conveniently, no R³ group is present (q=0).

It is further to be understood that any R⁴ group that may be present on the heterocyclyl group that is located at the 2-position on the pyrimidine ring may be located at any available position on said heterocyclyl group. Conveniently, when the R⁴ group is a (1-8C)alkyl group such as a methyl group, up to four such groups are present. Any two such groups may be located at the same position on said piperidine or tetrahydropyridine group. When each of s and t is 2, a piperidin-1-yl ring is formed. When two R⁴ groups on such a piperidin-1-yl ring together form a methylene, ethylene or trimethylene group, a suitable group so formed is, for example, a 3-azabicyclo[3.1.1]hept-3-yl, 6-azabicyclo[3.1.1]hept-6-yl, 2-azabicyclo[2.2.1]hept-2-yl, 2-azabicyclo[2.2.2]oct-2-yl, 3-azabicyclo[3.2.1]oct-3-yl or 8-azabicyclo[3.2.1]oct-8-yl group. When s is 1 and t is 2, a pyrrolidin-1-yl ring is formed. When two R⁴ groups on such a pyrrolidin-1-yl ring together form a methylene, ethylene or trimethylene group, a suitable group so formed is, for example, a 3-azabicyclo[2.1.1]hex-2-yl group. Conveniently, there is a single R⁴ group. More conveniently, no R⁴ group is present (r=0).

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

A suitable value for any one of the 'Q' groups (Q¹ to Q⁵) when it is aryl or for the aryl group within a 'Q' group is, for example, phenyl or naphthyl, preferably phenyl.

A suitable value for any one of the 'Q' groups (Q¹ to Q³) when it is (3-8C)cycloalkyl or for the (3-8C)cycloalkyl group within a 'Q' group is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptyl or cyclooctyl and a suitable value for any one of the 'Q' groups (Q¹ to Q³) when it is (3-8C)cycloalkenyl or for the (3-8C)cycloalkenyl group within a 'Q' group is, for example, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl or cyclooctenyl.

A suitable value for any one of the 'Q' groups (Q¹ to Q⁵) when it is heteroaryl or for the heteroaryl group within a 'Q' group is, for example, an aromatic 5- or 6-membered monocyclic ring or a 9- or 10-membered bicyclic ring with up to five ring heteroatoms selected from oxygen, nitrogen and sulphur, for example furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl,

benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxaliny, cinnolinyl or naphthyridinyl.

A suitable value for any one of the 'Q' groups (Q^1 to Q^5) when it is heterocyclyl or for the heterocyclyl group within a 'Q' group is, for example, a non-aromatic saturated or partially saturated 3 to 10 membered monocyclic or bicyclic ring with up to five heteroatoms selected from oxygen, nitrogen and sulphur, for example oxiranyl, oxetanyl, tetrahydrofuranyl, 5 tetrahydropyranyl, oxepanyl, tetrahydrothienyl, 1,1-dioxotetrahydrothienyl, tetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, azetidinyl, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, 10 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, oxazolidine, thiazolidine, 2-azabicyclo[2.2.1]heptyl, quinuclidinyl, chromanyl, isochromanyl, indolinyl, isoindolinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl, 15 tetrahydropyrimidinyl or tetrahydropyridazine, preferably tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl, piperidinyl or piperazinyl. A suitable value for such a group which bears 1 or 2 oxo or thioxo substituents is, for example, 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidinyl, 2-thioxoimidazolidinyl, 2-oxooxazolidinyl, 2-oxothiazolidinyl, 2-oxopiperidinyl, 4-oxo-1,4-dihydropyridinyl, 2,5-dioxopyrrolidinyl, 2,5-dioxoimidazolidinyl or 2,6-dioxopiperidinyl.

A suitable value for a 'Q' group when it is heteroaryl-(1-6C)alkyl is, for example, 20 heteroarylmethyl, 2-heteroarylethyl and 3-heteroarylpropyl. The invention comprises corresponding suitable values for 'Q' groups when, for example, rather than a heteroaryl-(1-6C)alkyl group, an aryl-(1-6C)alkyl, (3-8C)cycloalkyl-(1-6C)alkyl, (3-8C)cycloalkenyl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group is present.

Suitable values for any of the 'R' groups (R^1 to R^{17}), or for various groups within an R^1 , 25 R^3 or R^4 substituent, or for Q^1 , or for various groups within Q^1 include:-

for halogeno	fluoro, chloro, bromo and iodo;
for (1-8C)alkyl:	methyl, ethyl, propyl, isopropyl, <i>tert</i> -butyl, cyclobutyl, cyclohexyl, cyclohexylmethyl and 2-cyclopropylethyl;
for (2-8C)alkenyl:	vinyl, isopropenyl, allyl and but-2-enyl;
for (2-8C)alkynyl:	ethynyl, 2-propynyl and but-2-ynyl;
for (1-6C)alkoxy:	methoxy, ethoxy, propoxy, isopropoxy and butoxy;

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- for (2-6C)alkenyloxy: vinyloxy and allyloxy;
- for (2-6C)alkynyloxy: ethynyloxy and 2-propynyloxy;
- for (1-6C)alkylthio: methylthio, ethylthio and propylthio;
- for (1-6C)alkylsulphanyl: methylsulphanyl and ethylsulphanyl;
- 5 for (1-6C)alkylsulphonyl: methylsulphonyl and ethylsulphonyl;
- for (1-6C)alkylamino: methylamino, ethylamino, propylamino, isopropylamino and butylamino;
- for di-[(1-6C)alkyl]amino: dimethylamino, diethylamino, *N*-ethyl-*N*-methylamino and diisopropylamino;
- 10 for (1-6C)alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and *tert*-butoxycarbonyl;
- for (1-6C)alkoxycarbonylamino: methoxycarbonylamino, ethoxycarbonylamino and *tert*-butoxycarbonylamino;
- 15 for *N*-(1-6C)alkylcarbamoyl: *N*-methylcarbamoyl, *N*-ethylcarbamoyl and *N*-propylcarbamoyl;
- for *N,N*-di-[(1-6C)alkyl]carbamoyl: *N,N*-dimethylcarbamoyl, *N*-ethyl-*N*-methylcarbamoyl and *N,N*-diethylcarbamoyl;
- 20 for (2-6C)alkanoyl: acetyl, propionyl and isobutyryl;
- for (2-6C)alkanoyloxy: acetoxy and propionyloxy;
- for (2-6C)alkanoylamino: acetamido and propionamido;
- for *N*-(1-6C)alkyl-(2-6C)alkanoylamino: *N*-methylacetamido and *N*-methylpropionamido;
- for (3-6C)alkenoylamino: acrylamido, methacrylamido and crotonamido;
- for *N*-(1-6C)alkyl-(3-6C)alkenoylamino: *N*-methylacrylamido and *N*-methylcrotonamido;
- for (3-6C)alkynoylamino: propiolamido;
- 25 for *N*-(1-6C)alkyl-(3-6C)alkynoylamino: *N*-methylpropiolamido;
- for *N'*-(1-6C)alkylureido: *N'*-methylureido and *N'*-ethylureido;
- for *N',N'*-di-[(1-6C)alkyl]ureido: *N',N'*-dimethylureido and *N'*-methyl-*N'*-ethylureido;
- for *N*-(1-6C)alkylureido: *N*-methylureido and *N*-ethylureido;
- for *N,N'*-di-[(1-6C)alkyl]ureido: *N,N'*-dimethylureido, *N*-methyl-*N'*-ethylureido and *N*-ethyl-*N'*-methylureido;
- 30

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- for *N,N',N'*-di-[(1-6C)alkyl]ureido: *N,N',N'*-trimethylureido,
N-ethyl-*N',N'*-dimethylureido and
N-methyl-*N',N'*-diethylureido;
- for *N*-(1-6C)alkylsulphamoyl: *N*-methylsulphamoyl and *N*-ethylsulphamoyl;
- 5 for *N,N*-di-[(1-6C)alkyl]sulphamoyl: *N,N*-dimethylsulphamoyl;
- for (1-6C)alkanesulphonylamino: methanesulphonylamino and ethanesulphonylamino;
- for *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino: *N*-methylmethanesulphonylamino and
10 *N*-methylethanesulphonylamino;
for halogeno-(1-6C)alkyl: chloromethyl, 2-fluoroethyl, 2-chloroethyl,
1-chloroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl,
3-fluoropropyl, 3-chloropropyl, 3,3-difluoropropyl
and 3,3,3-trifluoropropyl;
- 15 for hydroxy-(1-6C)alkyl: hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and
3-hydroxypropyl;
- for mercapto-(1-6C)alkyl: mercaptomethyl, 2-mercaptoethyl, 1-mercaptoethyl
and 3-mercaptopropyl;
- 20 for (1-6C)alkoxy-(1-6C)alkyl: methoxymethyl, ethoxymethyl, 1-methoxyethyl,
2-methoxyethyl, 2-ethoxyethyl and
3-methoxypropyl;
- 25 for (1-6C)alkylthio-(1-6C)alkyl: methylthiomethyl, ethylthiomethyl,
2-methylthioethyl, 1-methylthioethyl and
3-methylthiopropyl;
- for (1-6C)alkylsulphinyl-(1-6C)alkyl: methylsulphinylmethyl, ethylsulphinylmethyl,
2-methylsulphinylethyl, 1-methylsulphinylethyl and
3-methylsulphinylpropyl;
- 30 for (1-6C)alkylsulphonyl-(1-6C)alkyl: methylsulphonylmethyl, ethylsulphonylmethyl,
2-methylsulphonylethyl, 1-methylsulphonylethyl and
3-methylsulphonylpropyl;
- for cyano-(1-6C)alkyl: cyanomethyl, 2-cyanoethyl, 1-cyanoethyl and
3-cyanopropyl;
- for amino-(1-6C)alkyl: aminomethyl, 2-aminoethyl, 1-aminoethyl,
3-aminopropyl, 1-aminopropyl and 5-aminopropyl;

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|----|--|---|
| | for (1-6C)alkylamino-(1-6C)alkyl: | methylaminomethyl, ethylaminomethyl,
1-methylaminoethyl, 2-methylaminoethyl,
2-ethylaminoethyl and 3-methylaminopropyl; |
| 5 | for di-[(1-6C)alkyl]amino-(1-6C)alkyl: | dimethylaminomethyl, diethylaminomethyl,
1-dimethylaminoethyl, 2-dimethylaminoethyl and
3-dimethylaminopropyl; |
| 10 | for (2-6C)alkanoylamino-(1-6C)alkyl: | acetamidomethyl, propionamidomethyl,
2-acetamidoethyl and 1-acetamidoethyl; |
| 15 | for N-(1-6C)alkyl-(2-6C)alkanoylamino-(1-6C)alkyl: | N-methylacetamidomethyl,
N-methylpropionamidomethyl,
2-(N-methylacetamido)ethyl and
1-(N-methylacetamido)ethyl; |
| 20 | for (1-6C)alkoxycarbonylamino-(1-6C)alkyl: | methoxycarbonylaminomethyl,
ethoxycarbonylaminomethyl,
<i>tert</i> -butoxycarbonylaminomethyl and
2-methoxycarbonylamoethyl; |
| 25 | for N'-(1-6C)alkylureido-(1-6C)alkyl: | N'-methylureidomethyl, 2-(N'-methylureido)ethyl
and 1-(N'-methylureido)ethyl; |
| 30 | for N',N'-di-[(1-6C)alkyl]ureido-(1-6C)alkyl: | N',N'-dimethylureidomethyl,
2-(N',N'-dimethylureido)ethyl and
1-(N',N'-dimethylureido)ethyl; |
| | for N-(1-6C)alkylureido-(1-6C)alkyl: | N-methylureidomethyl, 2-(N-methylureido)ethyl and
1-(N-methylureido)ethyl; |
| | for N,N'-di-[(1-6C)alkyl]ureido-(1-6C)alkyl: | N,N'-dimethylureidomethyl,
2-(N,N'-dimethylureido)ethyl and
1-(N,N'-dimethylureido)ethyl; |
| | for N,N',N'-di-[(1-6C)alkyl]ureido-(1-6C)alkyl: | N,N',N'-trimethylureidomethyl,
2-(N,N',N'-trimethylureido)ethyl and
1-(N,N',N'-trimethylureido)ethyl; |

for (1-6C)alkanesulphonylamino-(1-6C)alkyl: methanesulphonylaminomethyl,

2-(methanesulphonylamino)ethyl and

1-(methanesulphonylamino)ethyl; and

for *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino-(1-6C)alkyl:

5 *N*-methylmethanesulphonylaminomethyl,

2-(*N*-methylmethanesulphonylamino)ethyl and

1-(*N*-methylmethanesulphonylamino)ethyl.

A suitable value for $(R^1)_p$ when it is a (1-3C)alkylenedioxy group is, for example, methylenedioxy, ethylenedioxy, isopropylidenedioxy or ethylenedioxy and the oxygen atoms thereof occupy adjacent ring positions.

10 When, as defined hereinbefore, an R^1 group forms a group of the formula Q^2-X^2- and, for example, X^2 is a $OC(R^5)_2$ linking group, it is the carbon atom, not the oxygen atom, of the $OC(R^5)_2$ linking group which is attached to the benzimidazolyl ring and the oxygen atom is attached to the Q^2 group. Similarly, when, for example a CH_3 group within a R^1 substituent 15 bears a group of the formula $-X^3-Q^3$ and, for example, X^3 is a $C(R^6)_2O$ linking group, it is the carbon atom, not the oxygen atom, of the $C(R^6)_2O$ linking group which is attached to the CH_3 group and the oxygen atom is linked to the Q^3 group.

As defined hereinbefore, adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent may be optionally separated by the insertion into the chain of a group such as O, 20 $CON(R^{10})$ or $C\equiv C$. For example, insertion of an O atom into the alkylene chain within a 4-methoxybutoxy group gives rise to, for example, a 2-(2-methoxyethoxy)ethoxy group, for example, insertion of a $C\equiv C$ group into the ethylene chain within a 2-hydroxyethoxy group gives rise to a 4-hydroxybut-2-ynoxy group and, for example, insertion of a CONH group 25 into the ethylene chain within a 3-methoxypropoxy group gives rise to, for example, a 2-(2-methoxyacetamido)ethoxy group.

When, as defined hereinbefore, any CH , CH_2 or CH_3 group within a R^1 substituent 30 optionally bears on each said CH , CH_2 or CH_3 group one or more halogeno or (1-8C)alkyl substituents, there is suitably 1 halogeno or (1-8C)alkyl substituent present on each said CH group, there are suitably 1 or 2 such substituents present on each said CH_2 group and there are suitably 1, 2 or 3 such substituents present on each said CH_3 group.

When, as defined hereinbefore, any CH , CH_2 or CH_3 group within a R^1 substituent 35 optionally bears on each said CH , CH_2 or CH_3 group a substituent as defined hereinbefore,

suitable R¹ substituents so formed include, for example, hydroxy-substituted (1-8C)alkyl groups such as hydroxymethyl, 1-hydroxyethyl and 2-hydroxyethyl, hydroxy-substituted (1-6C)alkoxy groups such as 2-hydroxypropoxy and 3-hydroxypropoxy,
5 (1-6C)alkoxy-substituted (1-6C)alkoxy groups such as 2-methoxyethoxy and 3-ethoxypropoxy, hydroxy-substituted amino-(2-6C)alkoxy groups such as 3-amino-2-hydroxypropoxy, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkoxy groups such as 2-hydroxy-3-methylaminopropoxy, hydroxy-substituted di-[(1-6C)alkyl]amino-(2-6C)alkoxy groups such as 3-dimethylamino-2-hydroxypropoxy, hydroxy-substituted
10 amino-(2-6C)alkylamino groups such as 3-amino-2-hydroxypropylamino, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkylamino groups such as 2-hydroxy-3-methylaminopropylamino and hydroxy-substituted di-[(1-6C)alkyl]amino-(2-6C)alkylamino groups such as
15 3-dimethylamino-2-hydroxypropylamino.

It is further to be understood that when, as defined hereinbefore, any CH, CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH, CH₂ or CH₃ group a substituent as defined hereinbefore, such an optional substituent may be present on a CH, CH₂ or CH₃ group within the hereinbefore defined substituents that may be present on an aryl, heteroaryl or heterocyclyl group within a R¹ substituent. For example, if R¹ includes an aryl or heteroaryl group that is substituted by a (1-8C)alkyl group, the (1-8C)alkyl group may be optionally substituted on a CH, CH₂ or CH₃ group therein by one of the hereinbefore defined substituents therefor. For example, if R¹ includes a heteroaryl group that is substituted by, for example, a (1-6C)alkylamino-(1-6C)alkyl group, the terminal CH₃ group of the (1-6C)alkylamino group may be further substituted by, for example, a (1-6C)alkylsulphonyl group or a (2-6C)alkanoyl group. For example, the R¹ group may be a heteroaryl group such as a thienyl group that is substituted by a N-(2-methylsulphonylethyl)aminomethyl group such that R¹ is, for example, a 5-[N-(2-methylsulphonylethyl)aminomethyl]thien-2-yl group.
20 Further, for example, if R¹ includes a heterocyclyl group such as a piperidinyl or piperazinyl group that is substituted on a nitrogen atom thereof by, for example, a (2-6C)alkanoyl group, the terminal CH₃ group of the (2-6C)alkanoyl group may be further substituted by, for example, a di-[(1-6C)alkyl]amino group. For example, the R¹ group may be a
25 N-(2-dimethylaminoacetyl)piperidin-4-yl group or a 4-(2-dimethylaminoacetyl)piperazin-1-yl group.
30

Similar considerations apply to the attachments and substitutions within the $-X^1-Q^1$ group. For example, when, as defined hereinbefore, any CH, CH₂ or CH₃ group within a Q¹ group optionally bears on each said CH, CH₂ or CH₃ group a substituent as defined hereinbefore, suitable Q¹ groups so formed include, for example, hydroxy-substituted 5 amino-(1-6C)alkyl groups such as 1-amino-2-hydroxyethyl or 1-amino-2-hydroxypropyl, an (1-6C)alkoxy-substituted amino-(1-6C)alkyl groups such as 1-amino-2-methoxyethyl, a (1-6C)alkylamino-(1-6C)alkyl-substituted heteroaryl group such as a 5-[N-(2-methylsulphonyethyl)aminomethyl]thien-2-yl group, and a (2-6C)alkanoyl-10 substituted heterocyclic group such as a N-(2-dimethylaminoacetyl)piperidin-4-yl group or a 4-(2-dimethylaminoacetyl)piperazin-1-yl group.

Further, for example, it is defined hereinbefore that any aryl, (3-8C)cycloalkyl, (3-8C)cycloalkenyl, heteroaryl or heterocyclyl group within the Q¹ group may optionally bear 1, 2 or 3 substituents. Any such substituent may be present on any available position on said Q¹ group. For example, it is to be understood that, when there is a (3-8C)cycloalkyl, (3-8C)cycloalkenyl or heterocyclyl group within the Q¹ group, a substituent may be present on 15 any available position, including at the atom from which the (3-8C)cycloalkyl, (3-8C)cycloalkenyl or heterocyclyl group is linked to the remainder of the chemical structure. For example, a (3-8C)cycloalkyl group within the Q¹ group such as a cyclopropyl group that bears an amino substituent may thereby form a 1-aminocycloprop-1-yl group and a 20 heterocyclyl group within the Q¹ group such as a piperidin-4-yl group that bears a hydroxy substituent may thereby form a 4-hydroxypiperidin-4-yl group.

A suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for example, an acid-addition salt of a compound of the Formula I, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example, a salt of a compound of the Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine. A further suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for 25 example, a salt formed within the human or animal body after administration of a compound of the Formula I.

It is further to be understood that a suitable pharmaceutically-acceptable solvate of a compound of the Formula I also forms an aspect of the present invention. A suitable pharmaceutically-acceptable solvate is, for example, a hydrate such as a hemi-hydrate, a mono-hydrate, a di-hydrate or a tri-hydrate or an alternative quantity thereof.

5 It is further to be understood that a suitable pharmaceutically-acceptable pro-drug of a compound of the Formula I also forms an aspect of the present invention. Accordingly, 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
10 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
15 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
20 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
25 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);
- 5 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, 15 3-phthalidyl esters, (3-8C)cycloalkylcarbonyloxy-(1-6C)alkyl esters such as cyclopentylcarbonyloxyethyl 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 methoxycarbonyloxyethyl and 20 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 25 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 30 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 a carboxy group is, for example, an *in vivo* cleavable amide thereof, for example an amide formed with an amine such as ammonia, a (1-4C)alkylamine such as methylamine, a di-(1-4C)alkylamine such as dimethylamine, *N*-ethyl-*N*-methylamine or diethylamine, a (1-4C)alkoxy-(2-4C)alkylamine such as 2-methoxyethylamine, a phenyl-(1-4C)alkylamine such as benzylamine and amino acids such as glycine or an ester thereof.

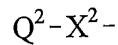
A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula I that possesses an amino group is, for example, an *in vivo* cleavable amide derivative thereof. Suitable pharmaceutically-acceptable amides from an amino group include, for example an amide formed with (1-10C)alkanoyl groups 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).

Particular novel compounds of the invention include, for example, pyrimidine derivatives of the Formula I, or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of p, R¹, R², q, R³, r, R⁴, s, t, X¹ and Q¹ has any of the meanings defined hereinbefore or in paragraphs (a) to (jjj) hereinafter :-

- (a) p is 0 or p is 1, 2 or 3, and each R¹ group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, hydroxy, mercapto, amino, carboxy, carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, *N,N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, *N*-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino,

N-(1-6C)alkyl-(3-6C)alkynoylamino, *N*-(1-6C)alkylsulphamoyl,
N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



5 wherein X^2 is a direct bond or is selected from O, S, $N(R^5)$, CO, wherein R^5 is hydrogen or (1-8C)alkyl, and Q^2 is aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or $(R^1)_p$ is (1-3C)alkylenedioxy,

and wherein any CH, CH_2 or CH_3 group within a R^1 substituent optionally bears on each
10 said CH, CH_2 or CH_3 group one or more halogeno or (1-8C)alkyl substituents and/or a substituent selected from hydroxy, mercapto, amino, cyano, carboxy, carbamoyl, ureido, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N,N*-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, 15 *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N*-(1-6C)alkylsulphamoyl, *N,N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-6C)alkanesulphonylamino,

and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within a substituent on R^1 optionally bears 1, 2 or 3 substituents, which may be the same or different, 20 selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo or thioxo substituents;

(b) p is 0 or p is 1 or 2, and each R^1 group, which may be the same or different, is selected 25 from halogeno, trifluoromethyl, cyano, hydroxy, amino, carboxy, carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, (2-6C)alkanoylamino and *N*-(1-6C)alkyl-(2-6C)alkanoylamino,

and wherein any CH, CH_2 or CH_3 group within a R^1 substituent optionally bears on each 30 said CH, CH_2 or CH_3 group 1, 2 or 3 halogeno or (1-8C)alkyl substituents and/or a substituent selected from hydroxy, amino, cyano, carboxy, carbamoyl, ureido, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl,

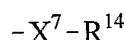
N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino and N-(1-6C)alkyl-(2-6C)alkanoylamino;

- (c) p is 0 or p is 1 or 2, and each R¹ group, which may be the same or different, is selected from fluoro, chloro, trifluoromethyl, cyano, hydroxy, amino, carboxy, carbamoyl, ureido, methyl, ethyl, propyl, vinyl, allyl, ethynyl, 2-propynyl, methoxy, ethoxy, propoxy, isopropoxy, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, methoxycarbonyl, ethoxycarbonyl, acetamido, propionamido, *N*-methylacetamido, *N*-methylpropionamido, hydroxymethyl, 1-hydroxyethyl, 1-hydroxy-1-methylethyl, 2-hydroxyethyl, 2-hydroxy-1-methylethyl, 2-hydroxypropyl, 1,1-dimethyl-2-hydroxyethyl, 2-hydroxy-2-methylpropyl, aminomethyl, 1-aminoethyl, 1-amino-1-methylethyl, 2-aminoethyl, 2-amino-1-methylethyl, 2-aminopropyl, 2-amino-1,1-dimethylethyl, 2-amino-2-methylpropyl, methylaminomethyl, 1-methylaminoethyl, 1-methylamino-1-methylethyl, 2-methylaminoethyl, 2-methylamino-1-methylethyl, 2-methylaminopropyl, 2-methylamino-1,1-dimethylethyl, 2-methylamino-2-methylpropyl, acetamidomethyl, 1-acetamidoethyl, 1-acetamido-1-methylethyl, 2-acetamidoethyl, 2-acetamido-1-methylethyl, 2-acetamidopropyl, 2-acetamido-1,1-dimethylethyl and 2-acetamido-2-methylpropyl;
- (d) p is 0 or p is 1 and the R¹ group is located at the 4-, 5- or 6-position on the benzimidazolyl group and is selected from fluoro, chloro, hydroxy, amino, methoxy, ethoxy, methylamino, ethylamino and acetamido;
- (e) p is 0 or p is 1 and the R¹ group is located at the 4-position on the benzimidazolyl group and is selected from fluoro, chloro, hydroxy, amino, methoxy, methylamino and acetamido;
- (f) p is 0 or p is 1 and the R¹ group is located at the 4-position on the benzimidazolyl group and is selected from hydroxy and methoxy;
- (g) p is 0;
- (h) R² is fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, hydroxy, amino, formamido, acetamido, propionamido, *N*-methylacetamido, methylamino, ethylamino, dimethylamino, diethylamino, hydroxymethyl or methoxymethyl;
- (i) R² is fluoromethyl, difluoromethyl, trifluoromethyl, hydroxy, amino, formamido or acetamido;
- (j) R² is difluoromethyl, trifluoromethyl, amino, formamido or acetamido;
- (k) R² is difluoromethyl;

- (l) q is 0 or q is 1, 2 or 3 and each R³ group, which may be the same or different, is methyl, ethyl or propyl;
- (m) q is 2 and the two R³ groups together form a methylene or ethylene group;
- (n) q is 0 or q is 1 or 2 and each R³ group is methyl;
- 5 (o) r is 0 or r is 1, 2, 3 or 4 and each R⁴ group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoylamino and N-(1-6C)alkyl-(2-6C)alkanoylamino, or two R⁴ groups together form a methylene or ethylene group;
- 10 (p) r is 0 or r is 1, 2, 3 or 4 and each R⁴ group, which may be the same or different, is methyl, ethyl or propyl;
- (q) r is 2 and the two R⁴ groups together form a methylene or ethylene group;
- (r) r is 0 or r is 1, 2, 3 or 4 and each R⁴ group is methyl;
- (s) s is 1 or 2 (especially 2);
- 15 (t) t is 2 or 3 (especially 2);
- (u) s is 2 and t is 2;
- (v) s is 1 and t is 3;
- (w) X¹ is selected from CO, N(R¹³)CO, CON(R¹³), N(R¹³)CON(R¹³), N(R¹³)COC(R¹³)₂O, N(R¹³)COC(R¹³)₂N(R¹³) and N(R¹³)COC(R¹³)₂N(R¹³)CO, wherein R¹³ is hydrogen or
- 20 (1-8C)alkyl;
- (x) X¹ is selected from CO, NHCO, N(Me)CO, CONH and CON(Me);
- (y) X¹ is CONH;
- (z) X¹ is NHCO;
- (aa) X¹ is CO;
- 25 (bb) Q¹ is (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, mercapto-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (1-6C)alkylthio-(1-6C)alkyl, (1-6C)alkylsulphanyl-(1-6C)alkyl, (1-6C)alkylsulphonyl-(1-6C)alkyl or (2-6C)alkanoylamino-(1-6C)alkyl,
- 30 or Q¹ is aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH, CH₂ or CH₃ group within the Q¹ group optionally bears on each said CH, CH₂ or CH₃ group one or more halogeno or (1-8C)alkyl substituents and/or a substituent selected from hydroxy, amino, cyano, carboxy, carbamoyl, ureido, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino and N-(1-6C)alkyl-(2-6C)alkanoylamino,

and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the Q¹ group optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, hydroxy, amino, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, or from a group of the formula :



wherein X⁷ is a direct bond or is selected from O and N(R¹⁵), wherein R¹⁵ is hydrogen or (1-8C)alkyl, and R¹⁴ is hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl,

and wherein any heterocyclyl group within the Q¹ group optionally bears 1 or 2 oxo or thioxo substituents;

(cc) Q¹ is (1-8C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (1-6C)alkylthio-(1-6C)alkyl or (2-6C)alkanoylamino-(1-6C)alkyl, or Q¹ is aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH, CH₂ or CH₃ group within the Q¹ group optionally bears on each said CH, CH₂ or CH₃ group 1, 2 or 3 halogeno or (1-8C)alkyl substituents and/or a substituent selected from hydroxy, amino, cyano, carboxy, carbamoyl, ureido, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino and N-(1-6C)alkyl-(2-6C)alkanoylamino,

and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the Q¹ group optionally bears 1 or 2 substituents, which may be the same or different, selected from

halogeno, trifluoromethyl, cyano, hydroxy, amino, (1-8C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, or from a group of the formula :

-X⁷-R¹⁴

wherein X⁷ is a direct bond and R¹⁴ is hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl,

5 cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or
di-[(1-6C)alkyl]amino-(1-6C)alkyl;

(dd) Q¹ is (1-8C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (1-6C)alkylsulphonyl-(1-6C)alkyl or (2-6C)alkanoylamino-(1-6C)alkyl, or Q¹ is aryl, 10 aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH, CH₂ or CH₃ group within the Q¹ group optionally bears on each said CH, CH₂ or CH₃ group a substituent selected from hydroxy, amino, cyano, carbamoyl, (1-6C)alkoxy, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, 15 (2-6C)alkanoyl, (2-6C)alkanoylamino and N-(1-6C)alkyl-(2-6C)alkanoylamino,

and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the Q¹ group optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-8C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, hydroxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl;

(ee) Q¹ is methyl, ethyl, propyl, isopropyl, butyl, pentyl, allyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, 2-ethoxyethyl, 3-ethoxypropyl, cyanomethyl, 2-cyanoethyl, 3-cyanopropyl, 1-cyano-1-methylethyl, 4-cyanobutyl, 25 5-cyanopentyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, 5-aminopentyl, methylaminomethyl, 2-methylaminooethyl, 3-methylaminopropyl, 4-methylaminobutyl, 5-methylaminopentyl, ethylaminomethyl, 2-ethylaminooethyl, 3-ethylaminopropyl, 4-ethylaminobutyl, 5-ethylaminopentyl, 1-isopropyl-1-methylaminomethyl, dimethylaminomethyl, 2-dimethylaminooethyl, 3-dimethylaminopropyl, 4-dimethylaminobutyl, 30 5-dimethylaminopentyl, diethylaminomethyl, 2-diethylaminooethyl, 3-diethylaminopropyl, 4-diethylaminobutyl, 5-diethylaminopentyl, 2-methylsulphonylethyl, 3-methylsulphonylpropyl, acetamidomethyl or 1-acetamidoethyl, or Q¹ is phenyl, benzyl,

2-phenylethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl,
cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl,
cycloheptylmethyl, furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl,
triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl,
5 furylmethyl, 2-furylethyl, thienylmethyl, 2-thienylethyl, oxazolylmethyl, 2-oxazolylethyl,
isoxazolylmethyl, 2-isoxazolylethyl, imidazolylmethyl, 2-imidazolylethyl, pyrazolylmethyl,
2-pyrazolylethyl, thiazolylmethyl, 2-thiazolylethyl, triazolylmethyl, 2-triazolylethyl,
oxadiazolylmethyl, 2-oxadiazolylethyl, thiadiazolylmethyl, 2-thiadiazolylethyl,
tetrazolylmethyl, 2-tetrazolylethyl, pyridylmethyl, 2-pyridylethyl, pyrazinylmethyl,
10 2-pyrazinylethyl, pyridazinylmethyl, 2-pyridazinylethyl, pyrimidinylmethyl, 2-pyrimidinylethyl,
pyrrolinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl,
piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, 2-azabicyclo[2.2.1]heptyl,
indolinyl, isoindolinyl, dihydropyridinyl, tetrahydrofuranylmethyl, tetrahydropyranyl, azetidinyl,
15 tetrahydrothiopyranymethyl, 1,3-dioxolanylmethyl, 1,4-dioxanymethyl, pyrrolinylmethyl,
2-(pyrrolinyl)ethyl, pyrrolidinylmethyl, 2-(pyrrolidinyl)ethyl, imidazolidinylmethyl,
pyrazolidinylmethyl, morpholinylmethyl, 2-(morpholinyl)ethyl,
tetrahydro-1,4-thiazinylmethyl, 2-(tetrahydro-1,4-thiazinyl)ethyl, piperidinylmethyl,
2-(piperidinyl)ethyl, homopiperidinylmethyl, 2-(homopiperidinyl)ethyl, piperazinylmethyl,
20 2-(piperazinyl)ethyl, homopiperazinylmethyl, 2-(homopiperazinyl)ethyl or
2-azabicyclo[2.2.1]heptylmethyl,

and wherein any CH, CH₂ or CH₃ group within the Q¹ group optionally bears on each
said CH, CH₂ or CH₃ group a substituent selected from hydroxy, amino, cyano, carbamoyl,
methoxy, ethoxy, methylsulphonyl, methylamino, ethylamino, dimethylamino, diethylamino,
25 methoxycarbonyl, ethoxycarbonyl, N-methylcarbamoyl, N-ethylcarbamoyl,
N-isopropylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, acetyl, propionyl,
butyryl, pivaloyl, acetamido, propionamido and N-methylacetamido,

and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the Q¹
group optionally bears 1 or 2 substituents, which may be the same or different, selected from
30 fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methoxy, ethoxy,
methylamino, dimethylamino, hydroxymethyl, 2-hydroxyethyl, methoxymethyl,

2-methoxyethyl, cyanomethyl, 2-cyanoethyl, aminomethyl, 2-aminoethyl,
methylaminomethyl, 2-methylaminoethyl, dimethylaminomethyl and 2-dimethylaminoethyl;
(ff) Q¹ is methyl, ethyl, propyl, isopropyl, butyl, pentyl, allyl, 2-methoxyethyl,
3-methoxypropyl, 2-ethoxyethyl, 3-ethoxypropyl, cyanomethyl, 2-cyanoethyl, 3-cyanopropyl,
5 1-cyano-1-methylethyl, 4-cyanobutyl, 5-cyanopentyl, aminomethyl, 2-aminoethyl,
3-aminopropyl, 4-aminobutyl, 5-aminopentyl, methylaminomethyl, 2-methylaminoethyl,
3-methylaminopropyl, 4-methylaminobutyl, 5-methylaminopentyl, ethylaminomethyl,
2-ethylaminoethyl, 3-ethylaminopropyl, 4-ethylaminobutyl, 5-ethylaminopentyl,
dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 4-dimethylaminobutyl,
10 5-dimethylaminopentyl, diethylaminomethyl, 2-diethylaminoethyl, 3-diethylaminopropyl,
4-diethylaminobutyl, 5-diethylaminopentyl, 2-methylsulphonylethyl or acetamidomethyl, or
Q¹ is phenyl, benzyl, 2-phenylethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, furyl, thieryl,
oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl,
15 tetrazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, furylmethyl, thiethylmethyl,
oxazolylmethyl, isoxazolylmethyl, imidazolylmethyl, 2-imidazolylethyl, pyrazolylmethyl,
thiazolylmethyl, triazolylmethyl, oxadiazolylmethyl, thiadiazolylmethyl, tetrazolylmethyl,
pyridylmethyl, 2-pyridylethyl, pyrazinylmethyl, 2-pyrazinylethyl, pyridazinylmethyl,
2-pyridazinylethyl, pyrimidinylmethyl, 2-pyrimidinylethyl, tetrahydrofuranyl,
20 tetrahydropyranyl, tetrahydrothiopyranyl, azetidinyl, pyrrolinyl, pyrrolidinyl, morpholinyl,
tetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl,
indolinyl, isoindolinyl, tetrahydrofuranylmethyl, tetrahydropyranylmethyl,
1,3-dioxolanyl methyl, 1,4-dioxanyl methyl, pyrrolidinylmethyl, 2-(pyrrolidinyl)ethyl,
morpholinylmethyl, 2-(morpholinyl)ethyl, piperidinylmethyl, 2-(piperidinyl)ethyl,
25 homopiperidinylmethyl, piperazinylmethyl, 2-(piperazinyl)ethyl or homopiperazinylmethyl,
and wherein any CH, CH₂ or CH₃ group within the Q¹ group optionally bears on each
said CH, CH₂ or CH₃ group a substituent selected from hydroxy, amino, cyano, carbamoyl,
methoxy, ethoxy, methylsulphonyl, methylamino, dimethylamino, methoxycarbonyl,
ethoxycarbonyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-isopropylcarbamoyl,
30 N,N-dimethylcarbamoyl, acetyl, propionyl, pivaloyl, acetamido and N-methylacetamido,
and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the Q¹
group optionally bears 1 or 2 substituents, which may be the same or different, selected from

fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, methoxy, methylamino and dimethylamino and any such aryl, (3-8C)cycloalkyl, heteroaryl or heterocycl group within the Q¹ group optionally bears a substituent selected from hydroxymethyl, methoxymethyl, cyanomethyl, aminomethyl, methylaminomethyl and dimethylaminomethyl;

- 5 (gg) Q¹ is aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, 5-aminopentyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, 5-methylaminopentyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 4-dimethylaminobutyl or 5-dimethylaminopentyl, or Q¹ is phenyl, benzyl, 2-phenylethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclohexylmethyl, 10 thienyl, imidazolyl, thiazolyl, thiadiazolyl, thienylmethyl, imidazolylmethyl, thiazolylmethyl, thiadiazolylmethyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, indolinyl, isoindolinyl, pyrrolidinylmethyl, 2-(pyrrolidinyl)ethyl, morpholinylmethyl, 2-(morpholinyl)ethyl, piperidinylmethyl, 2-(piperidinyl)ethyl, 15 homopiperidinylmethyl, piperazinylmethyl, 2-(piperazinyl)ethyl, homopiperazinylmethyl or 2-azabicyclo[2.2.1]heptylmethyl,

and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocycl group within the Q¹ group optionally bears a substituent selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, methoxy, methylamino and dimethylamino and any such aryl,

- 20 (3-8C)cycloalkyl, heteroaryl or heterocycl group within the Q¹ group optionally bears a further substituent selected from aminomethyl, methylaminomethyl and dimethylaminomethyl;

- (hh) Q¹ is aminomethyl, 1-aminoethyl, 1-amino-1-methylethyl, methylaminomethyl, 1-methylaminoethyl, 1-methylamino-1-methylethyl, acetamidoethyl, 1-acetamidoethyl or 25 1-acetamido-1-methylethyl;

(ii) the X¹-Q¹ group is an α-amino carbonyl group;

(jj) the X¹-Q¹ group is a naturally-occurring α-amino carbonyl group;

- (kk) the X¹-Q¹ group is selected from glycyl, sarcosyl, N-ethylglycyl, N,N-dimethylglycyl, glycylglycyl, L-alanyl, 2-methylalanyl, N-methylalanyl, β-alanyl, (2S)-2-aminobutanoyl, 30 L-valyl, N-methyl-L-valyl, 2-aminopent-4-yenyl, 2-aminopentanoyl, L-isoleucyl, L-leucyl, 2-methyl-L-leucyl, N-methyl-L-leucyl, seryl, O-methyl-L-seryl, N-methyl-L-seryl, O-methyl-L-homoseryl, L-threonyl, S-methyl-L-cysteinyl, S-methyl-L-homocysteinyl,

L-methionyl, N-methyl-L-lysyl, N-methyl-L-ornithyl, D-asparaginyl, D-glutaminyl, L-tyrosyl, proyl and histidyl;

(ll) the X¹-Q¹ group is an α -amino carboxamido group;

(mm) the X¹-Q¹ group is a naturally-occurring α -amino carboxamido group;

5 (nn) the X¹-Q¹ group is selected from glycylamino, sarcosylamino,

(N,N-dimethylglycyl)amino, glycylglycylamino, L-alanylalmino, 2-methylalanylalmino,

(N-methylalanyl)amino, (2S)-2-aminobutanoylamino, L-valylamino,

(N-methyl-L-valyl)amino, 2-aminopent-4-ynoylamino, 2-aminopentanoylamino,

L-isoleucylamino, L-leucylamino, 2-methyl-L-leucylamino, (N-methyl-L-leucyl)amino,

10 serylamino, (O-methyl-L-seryl)amino, (N-methyl-L-seryl)amino,

(O-methyl-L-homoseryl)amino, L-threonylamino, (S-methyl-L-cysteinyl)amino,

(S-methyl-L-homocysteinyl)amino, L-methionylamino, (N-methyl-L-lysyl)amino,

(N-methyl-L-ornithyl)amino, D-asparaginylamino, D-glutaminylamino, L-tyrosylamino,

prolylamino and histidylamino;

15 (oo) the 5-position on the pyrimidine ring may bear a methyl group;

(pp) the 5-position on the pyrimidine ring is unsubstituted;

(qq) q is 0 or q is 1 and the R³ group is methyl;

(rr) q is 0;

20 (ss) r is 0, or r is 1 or 2 and each R⁴ group, which may be the same or different, is a (1-4C)alkyl group, or r is 2 and the two R⁴ groups together form a methylene, ethylene or trimethylene group;

(tt) r is 0, or r is 2 and each R⁴ group, which may be the same or different, is a (1-4C)alkyl group (especially a methyl group), or r is 2 and the two R⁴ groups together form an ethylene group;

25 (uu) r is 0;

(vv) r is 2 and each R⁴ group, which may be the same or different, is a (1-4C)alkyl group (especially a methyl group);

(ww) r is 2 and the two R⁴ groups together form an ethylene group;

(xx) X¹ is a direct bond or is selected from CO, N(R¹³)CO, CON(R¹³) and

30 N(R¹³)COC(R¹³)₂N(R¹³)CO, wherein R¹³ is hydrogen or (1-2C)alkyl (such as methyl);

(yy) X¹ is a direct bond or is selected from CO, NHCO, CONH and NHCOCH₂NHCO;

(zz) X¹ is a direct bond or is NHCO;

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(aaa) X^1 is a direct bond;

(bbb) Q^1 is (1-8C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, aryl-(1-6C)alkyl or heterocyclyl,

and wherein any CH, CH₂ or CH₃ group within the Q^1 group optionally bears on each
 5 said CH, CH₂ or CH₃ group one or more halogeno or (1-8C)alkyl substituents and/or a
 substituent selected from hydroxy, mercapto, amino, cyano, carboxy, carbamoyl, ureido, (1-
 6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino,
 di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N,N*-di-[(1-
 6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-
 10 6C)alkyl-(2-6C)alkanoylamino, *N'*-(1-6C)alkylureido, *N',N'*-di-[(1-6C)alkyl]ureido, *N*-(1-
 6C)alkylureido, *N,N'*-di-[(1-6C)alkyl]ureido, *N,N',N'*-tri-[(1-6C)alkyl]ureido, *N*-(1-
 6C)alkylsulphamoyl, *N,N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-
 6C)alkyl-(1-6C)alkanesulphonylamino,

and wherein any aryl or heterocyclyl group within the Q^1 group optionally bears 1, 2 or 3
 15 substituents, which may be the same or different, selected from halogeno, trifluoromethyl,
 cyano, nitro, hydroxy, amino, carboxy, carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-
 8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenylloxy, (2-6C)alkynylloxy, (1-6C)alkylthio, (1-
 6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-
 6C)alkoxycarbonyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, *N*-(1-6C)alkylcarbamoyl, *N,N*-di-[(1-
 20 6C)alkyl]carbamoyl, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, *N'*-(1-
 6C)alkylureido, *N',N'*-di-[(1-6C)alkyl]ureido, *N*-(1-6C)alkylureido, *N,N'*-di-[(1-
 6C)alkyl]ureido, *N,N',N'*-tri-[(1-6C)alkyl]ureido, *N*-(1-6C)alkylsulphamoyl, *N,N*-di-[(1-
 6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and *N*-(1-6C)alkyl-(1-
 6C)alkanesulphonylamino, or from a group of the formula :

$-X^7-R^{14}$

wherein X^7 is a direct bond or is selected from O and N(R^{15}), wherein R^{15} is hydrogen or (1-
 8C)alkyl, and R^{14} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl,
 cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or
 di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :

$-X^8-Q^5$

wherein X^8 is a direct bond or is selected from O, CO and N(R^{17}), wherein R^{17} is hydrogen or
 (1-8C)alkyl, and Q^5 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl

or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, hydroxy, (1-8C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within the Q¹ group optionally bears 1 or 2 oxo or thioxo substituents,

5 and wherein adjacent carbon atoms in any (2-6C)alkylene chain within the Q¹ group are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R¹⁶), N(R¹⁶)CO, CON(R¹⁶), N(R¹⁶)CON(R¹⁶), CO, CH(OR¹⁶), N(R¹⁶)SO₂, SO₂N(R¹⁶), CH=CH and C≡C wherein R¹⁶ is hydrogen or (1-8C)alkyl;

(ccc) Q¹ is amino-(1-2C)alkyl, aryl-(1-2C)alkyl or heterocyclyl, and wherein any CH or CH₂ group within the Q¹ group optionally bears on each said CH or CH₂ group one or more (1-6C)alkylamino substituents;

(ddd) Q¹ is aminomethyl, 2-aminoethyl, 2-phenylethyl, pyrrolidinyl or piperidinyl,

and wherein any CH or CH₂ group within the Q¹ group optionally bears on each said CH or CH₂ group a substituent selected from hydroxy, amino, cyano, carbamoyl, methoxy, ethoxy, methylsulphonyl, methylamino, ethylamino, dimethylamino, diethylamino, methoxycarbonyl, ethoxycarbonyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-isopropylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, acetyl, propionyl, butyryl, pivaloyl, acetamido, propionamido and N-methylacetamido,

20 and wherein any phenyl, pyrrolidinyl or piperidinyl group within the Q¹ group optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methoxy, ethoxy, methylamino, dimethylamino, hydroxymethyl, 2-hydroxyethyl, methoxymethyl, 2-methoxyethyl, cyanomethyl, 2-cyanoethyl, aminomethyl, 2-aminoethyl, methylaminomethyl, 2-methylaminoethyl, dimethylaminomethyl and 2-dimethylaminoethyl;

(eee) Q¹ is aminomethyl, 2-aminoethyl, 2-phenylethyl, pyrrolidinyl or piperidinyl,

and wherein any CH or CH₂ group within the Q¹ group optionally bears on each said CH or CH₂ group a substituent selected from methylamino, ethylamino, dimethylamino and diethylamino (especially methylamino);

(fff) X¹ is NHCO and Q¹ is amino-(1-6C)alkyl, aryl-(1-6C)alkyl or heterocyclyl (especially aminomethyl, 2-phenylethyl, pyrrolidinyl or piperidinyl),

30 and wherein any CH or CH₂ group within the Q¹ group optionally bears on each said CH or CH₂ group a methylamino substituent;

(ggg) X^1 is a direct bond and Q^1 is amino-(1-6C)alkyl (especially amino-(1-2C)alkyl, such as 2-aminoethyl);

(hhh) X^1 is CONH and Q^1 is amino-(1-6C)alkyl (especially amino-(1-2C)alkyl, such as 2-aminoethyl);

5 (iii) X^1 is NHCOCH₂NHCO and Q^1 is heterocyclyl (especially pyrrolidinyl or piperidinyl);

(jjj) X^1 is CO and Q^1 is amino-(1-6C)alkyl, aryl-(1-6C)alkyl or heterocyclyl (especially aminomethyl, 2-phenylethyl, pyrrolidinyl or piperidinyl),

and wherein any CH or CH₂ group within the Q^1 group optionally bears on each said CH or CH₂ group a methylamino substituent.

10 "Me" herein represents methyl.

A particular compound of the invention is a pyrimidine derivative of the Formula I wherein :-

p is 0 or p is 1 and the R¹ group is located at the 4-, 5- or 6-position on the benzimidazolyl group and is selected from fluoro, chloro, hydroxy, amino, methoxy, ethoxy, methylamino, ethylamino and acetamido;

15 R² is fluoromethyl, difluoromethyl, trifluoromethyl, hydroxy, amino, formamido or acetamido;

q is 0 or q is 1 or 2 and each R³ group is methyl;

r is 0, or r is 1, 2, 3 or 4 and each R⁴ group, which may be the same or different, is

20 methyl, ethyl or propyl; or r is 2 and the two R⁴ groups together form a methylene or ethylene group;

s is 2 and t is 2, or s is 1 and t is 3;

X¹ is selected from CO, NHCO, N(Me)CO, CONH and CON(Me); and

Q¹ is methyl, ethyl, propyl, isopropyl, butyl, pentyl, allyl, 2-methoxyethyl,

25 3-methoxypropyl, 2-ethoxyethyl, 3-ethoxypropyl, cyanomethyl, 2-cyanoethyl, 3-cyanopropyl, 1-cyano-1-methylethyl, 4-cyanobutyl, 5-cyanopentyl, aminomethyl, 2-aminoethyl,

3-aminopropyl, 4-aminobutyl, 5-aminopentyl, methylaminomethyl, 2-methylaminooethyl,

3-methylaminopropyl, 4-methylaminobutyl, 5-methylaminopentyl, ethylaminomethyl,

2-ethylaminooethyl, 3-ethylaminopropyl, 4-ethylaminobutyl, 5-ethylaminopentyl,

30 dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 4-dimethylaminobutyl,

5-dimethylaminopentyl, diethylaminomethyl, 2-diethylaminoethyl, 3-diethylaminopropyl,

4-diethylaminobutyl, 5-diethylaminopentyl, 2-methylsulphonylethyl or acetamidomethyl, or

Q¹ is phenyl, benzyl, 2-phenylethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, furylmethyl, thienylmethyl, 5 oxazolylmethyl, isoxazolylmethyl, imidazolylmethyl, 2-imidazolylethyl, pyrazolylmethyl, thiazolylmethyl, triazolylmethyl, oxadiazolylmethyl, thiadiazolylmethyl, tetrazolylmethyl, pyridylmethyl, 2-pyridylethyl, pyrazinylmethyl, 2-pyrazinylethyl, pyridazinylmethyl, 2-pyridazinylethyl, pyrimidinylmethyl, 2-pyrimidinylethyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, azetidinyl, pyrrolinyl, pyrrolidinyl, morpholinyl, 10 tetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, indolinyl, isoindolinyl, tetrahydrofuranylmethyl, tetrahydropyranylmethyl, 1,3-dioxolanylmethyl, 1,4-dioxanyl methyl, pyrrolidinylmethyl, 2-(pyrrolidinyl)ethyl, morpholinylmethyl, 2-(morpholinyl)ethyl, piperidinylmethyl, 2-(piperidinyl)ethyl, homopiperidinylmethyl, piperazinylmethyl, 2-(piperazinyl)ethyl or homopiperazinylmethyl, 15 and wherein any CH, CH₂ or CH₃ group within the Q¹ group optionally bears on each said CH, CH₂ or CH₃ group a substituent selected from hydroxy, amino, cyano, carbamoyl, methoxy, ethoxy, methylsulphonyl, methylamino, dimethylamino, methoxycarbonyl, ethoxycarbonyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-isopropylcarbamoyl, N,N-dimethylcarbamoyl, acetyl, propionyl, pivaloyl, acetamido and N-methylacetamido, 20 and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the Q¹ group optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, methoxy, methylamino and dimethylamino and any such aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the Q¹ group optionally bears a substituent selected from hydroxymethyl, methoxymethyl, cyanomethyl, aminomethyl, methylaminomethyl and dimethylaminomethyl; 25 and the 5-position on the pyrimidine ring is unsubstituted; or a pharmaceutically-acceptable salt thereof.

A further particular compound of the invention is a pyrimidine derivative of the Formula I wherein :-

30 p is 0;
R² is difluoromethyl;
q is 0 or q is 1 and the R³ group is methyl;

r is 0, or r is 1 or 2 and each R⁴ group, which may be the same or different, is methyl, ethyl or propyl (especially each R⁴ group is methyl); or r is 2 and the two R⁴ groups together form an ethylene group;

s is 2 and t is 2;

5 X¹ is a direct bond or is selected from CO, NHCO, CONH and NHCOCH₂NHCO (especially a direct bond or NHCO); and

Q¹ is methyl, ethyl, propyl, isopropyl, butyl, pentyl, allyl, 2-methoxyethyl, 3-methoxypropyl, 2-ethoxyethyl, 3-ethoxypropyl, cyanomethyl, 2-cyanoethyl, 3-cyanopropyl, 1-cyano-1-methylethyl, 4-cyanobutyl, 5-cyanopentyl, aminomethyl, 2-aminoethyl, 10 3-aminopropyl, 4-aminobutyl, 5-aminopentyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, 5-methylaminopentyl, ethylaminomethyl, 2-ethylaminoethyl, 3-ethylaminopropyl, 4-ethylaminobutyl, 5-ethylaminopentyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 4-dimethylaminobutyl, 5-dimethylaminopentyl, diethylaminomethyl, 2-diethylaminoethyl, 3-diethylaminopropyl, 15 4-diethylaminobutyl, 5-diethylaminopentyl, 2-methylsulphonyethyl or acetamidomethyl, or Q¹ is phenyl, benzyl, 2-phenylethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, furylmethyl, thienylmethyl, 20 20 oxazolylmethyl, isoxazolylmethyl, imidazolylmethyl, 2-imidazolylethyl, pyrazolylmethyl, thiazolylmethyl, triazolylmethyl, oxadiazolylmethyl, thiadiazolylmethyl, tetrazolylmethyl, pyridylmethyl, 2-pyridylethyl, pyrazinylmethyl, 2-pyrazinylethyl, pyridazinylmethyl, 2-pyridazinylethyl, pyrimidinylmethyl, 2-pyrimidinylethyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, azetidinyl, pyrrolinyl, pyrrolidinyl, morpholinyl, 25 25 tetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, indolinyl, isoindolinyl, tetrahydrofuranyl methyl, tetrahydropyranylmethyl, 1,3-dioxolanyl methyl, 1,4-dioxanyl methyl, pyrrolidinylmethyl, 2-(pyrrolidinyl)ethyl, morpholinylmethyl, 2-(morpholinyl)ethyl, piperidinylmethyl, 2-(piperidinyl)ethyl, homopiperidinylmethyl, piperazinylmethyl, 2-(piperazinyl)ethyl or homopiperazinylmethyl, and wherein any CH, CH₂ or CH₃ group within the Q¹ group optionally bears on each said CH, CH₂ or CH₃ group a substituent selected from hydroxy, amino, cyano, carbamoyl, methoxy, ethoxy, methylsulphonyl, methylamino, dimethylamino, methoxycarbonyl,

ethoxycarbonyl, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N*-isopropylcarbamoyl, *N,N*-dimethylcarbamoyl, acetyl, propionyl, pivaloyl, acetamido and *N*-methylacetamido,

and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the Q¹ group optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, methoxy, methylamino and dimethylamino and any such aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the Q¹ group optionally bears a substituent selected from hydroxymethyl, methoxymethyl, cyanomethyl, aminomethyl, methylaminomethyl and dimethylaminomethyl;

and the 5-position on the pyrimidine ring is unsubstituted;

or a pharmaceutically-acceptable salt thereof.

A further particular compound of the invention is a pyrimidine derivative of the Formula I wherein :-

p is 0;

R² is difluoromethyl;

q is 0 or q is 1 and the R³ group is methyl;

r is 0, or r is 1 or 2 and each R⁴ group, which may be the same or different, is methyl, ethyl or propyl (especially each R⁴ group is methyl); or r is 2 and the two R⁴ groups together form an ethylene group;

s is 2 and t is 2;

X¹ is a direct bond or is selected from CO, NHCO, CONH and NHCOCH₂NHCO (especially a direct bond or NHCO); and

Q¹ is aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, 5-aminopentyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, 5-methylaminopentyl, ethylaminomethyl, 2-ethylaminoethyl, 3-ethylaminopropyl, 4-ethylaminobutyl, 5-ethylaminopentyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 4-dimethylaminobutyl, 5-dimethylaminopentyl, diethylaminomethyl, 2-diethylaminoethyl, 3-diethylaminopropyl, 4-diethylaminobutyl or 5-diethylaminopentyl, or Q¹ is benzyl, 2-phenylethyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl, azetidinyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, indolinyl or isoindolinyl,

and wherein any CH, CH₂ or CH₃ group within the Q¹ group optionally bears on each said CH, CH₂ or CH₃ group a substituent selected from hydroxy, amino, cyano, carbamoyl,

methoxy, ethoxy, methylsulphonyl, methylamino, dimethylamino, methoxycarbonyl, ethoxycarbonyl, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N*-isopropylcarbamoyl, *N,N*-dimethylcarbamoyl, acetyl, propionyl, pivaloyl, acetamido and *N*-methylacetamido,

and wherein any aryl or heterocyclyl group within the Q¹ group optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, methoxy, methylamino and dimethylamino and any such aryl or heterocyclyl group within the Q¹ group optionally bears a substituent selected from hydroxymethyl, methoxymethyl, cyanomethyl, aminomethyl, methylaminomethyl and dimethylaminomethyl;

10 and the 5-position on the pyrimidine ring is unsubstituted;
or a pharmaceutically-acceptable salt thereof.

A further particular compound of the invention is a pyrimidine derivative of the Formula I wherein :-

p is 0;

15 R² is difluoromethyl;

q is 0 or q is 1 and the R³ group is methyl;

r is 0;

s is 2 and t is 2;

X¹ is a direct bond or is NHCO; and

20 Q¹ is aminomethyl, 2-aminoethyl, 2-phenylethyl, pyrrolidinyl or piperidinyl,

and wherein any CH, CH₂ or CH₃ group within the Q¹ group optionally bears on each said CH, CH₂ or CH₃ group a substituent selected from methylamino and dimethylamino (especially methylamino)

and wherein any aryl or heterocyclyl group within the Q¹ group optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, methoxy, methylamino and dimethylamino and any such aryl or heterocyclyl group within the Q¹ group optionally bears a substituent selected from hydroxymethyl, methoxymethyl, cyanomethyl, aminomethyl, methylaminomethyl and dimethylaminomethyl;

30 and the 5-position on the pyrimidine ring is unsubstituted;
or a pharmaceutically-acceptable salt thereof.

A further particular compound of the invention is a pyrimidine derivative of the Formula I wherein :-

p is 0 or p is 1 and the R¹ group is located at the 4-, 5- or 6-position on the benzimidazolyl group and is selected from fluoro, chloro, hydroxy, amino, methoxy, ethoxy, 5 methylamino, ethylamino and acetamido;

R² is fluoromethyl, difluoromethyl, trifluoromethyl, hydroxy, amino, formamido or acetamido;

q is 0 or q is 1 or 2 and each R³ group is methyl;

r is 0, or r is 1, 2, 3 or 4 and each R⁴ group, which may be the same or different, is 10 methyl, ethyl or propyl; or r is 2 and the two R⁴ groups together form a methylene or ethylene group;

s is 2 and t is 2, or s is 1 and t is 3; and

the X¹-Q¹ group is selected from glycylamino, sarcosylamino,

(N,N-dimethylglycyl)amino, glycylglycylamino, L-alanylalmino, 2-methylalanylalmino,

15 (N-methylalanyl)amino, (2S)-2-aminobutanoylamino, L-valylalmino,

(N-methyl-L-valyl)amino, 2-aminopent-4-ynoylamino, 2-aminopentanoylamino,

L-isoleucylamino, L-leucylamino, 2-methyl-L-leucylamino, (N-methyl-L-leucyl)amino,

serylamino, (O-methyl-L-seryl)amino, (N-methyl-L-seryl)amino,

(O-methyl-L-homoserl)amino, L-threonylamino, (S-methyl-L-cysteinyl)amino,

20 (S-methyl-L-homocysteinyl)amino, L-methionylamino, (N-methyl-L-lysyl)amino,

(N-methyl-L-ornithyl)amino, D-asparaginylamino, D-glutaminylamino, L-tyrosylamino,

prolylamino and histidylamino;

and the 5-position on the pyrimidine ring is unsubstituted;

or a pharmaceutically-acceptable salt thereof.

25 A further particular compound of the invention is a pyrimidine derivative of the Formula I wherein :-

p is 0 or p is 1 and the R¹ group is located at the 4-position on the benzimidazolyl group and is selected from hydroxy and methoxy;

R² is difluoromethyl;

30 q is 0;

r is 0, or r is 1 or 2 and each R⁴ group is methyl, or r is 2 and the two R⁴ groups together form a methylene or ethylene group;

s is 2 and t is 2, or s is 1 and t is 3;

X¹ is CO, CONH or CON(Me); and

Q¹ is methyl, ethyl, propyl, isopropyl, 2-ethoxyethyl, 3-ethoxypropyl, cyanomethyl, 2-cyanoethyl, aminomethyl, 2-aminoethyl, methylaminomethyl, 2-methylaminoethyl,
5 ethylaminomethyl, 2-ethylaminoethyl, dimethylaminomethyl, 2-dimethylaminoethyl, 4-dimethylaminobutyl, 2-methylsulphonyethyl or acetamidomethyl, or Q¹ is phenyl, benzyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, imidazol-2-yl, imidazol-4-yl, pyrazol-3-yl, thiazol-5-yl, 1,2,3-triazol-5-yl, tetrazol-5-yl, pyridin-2-yl,
10 pyridin-3-yl, pyridin-4-yl, pyrazin-2-yl, pyridazin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, thien-3-ylmethyl, oxazol-4-ylmethyl, isoxazol-3-ylmethyl, isoxazol-4-ylmethyl, imidazol-1-ylmethyl, imidazol-2-ylmethyl, 2-imidazol-1-ylethyl, 2-imidazol-2-ylethyl, 2-imidazol-4-ylethyl, pyrazol-1-ylmethyl, pyrazol-3-ylmethyl, 1,2,3-triazol-1-ylmethyl, 1,2,3-triazol-4-ylmethyl, 1,2,4-oxadiazol-3-ylmethyl, 1,2,3-thiadiazol-3-ylmethyl,
15 tetrazol-1-ylmethyl, tetrazol-5-ylmethyl, pyridin-2-ylmethyl, pyridin-3-ylmethyl, pyridin-4-ylmethyl, 2-pyridin-2-ylethyl, 2-pyridin-3-ylethyl, 2-pyridin-4-ylethyl, pyrazin-2-ylmethyl, 2-pyrazin-2-ylethyl, pyridazin-4-ylmethyl, 2-pyridazin-4-ylethyl, pyrimidin-2-ylmethyl, pyrimidin-4-ylmethyl, 2-pyrimidin-2-ylethyl, 2-pyrimidin-4-ylethyl, tetrahydrofuran-2-yl, tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, azetidin-2-yl,
20 3-pyrrolin-2-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, morpholino, morpholin-2-yl, piperidino, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, isoindolin-1-yl, tetrahydrofuran-2-ylmethyl, tetrahydropyran-4-ylmethyl, 1,3-dioxolan-2-ylmethyl, 1,4-dioxan-2-ylmethyl, pyrrolidin-2-ylmethyl, piperidin-2-ylmethyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl, 2-(piperidin-4-yl)ethyl, piperidin-4-yloxymethyl, piperazin-1-ylmethyl
25 or 2-(piperazin-1-yl)ethyl,

and wherein any CH, CH₂ or CH₃ group within the Q¹ group optionally bears on each said CH, CH₂ or CH₃ group a substituent selected from hydroxy, carbamoyl, methoxycarbonyl, ethoxycarbonyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-isopropylcarbamoyl, N,N-dimethylcarbamoyl, acetyl, propionyl, pivaloyl, acetamido and N-methylacetamido,

30 and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the Q¹ group optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, hydroxy, amino, carbamoyl, methyl, methylamino, dimethylamino,

hydroxymethyl, methoxymethyl, cyanomethyl, aminomethyl, methylaminomethyl and dimethylaminomethyl;

and the 5-position on the pyrimidine ring is unsubstituted;
or a pharmaceutically-acceptable salt thereof.

5 A further particular compound of the invention is a pyrimidine derivative of the Formula I wherein :-

p is 0 or p is 1 and the R¹ group is located at the 4-position on the benzimidazolyl group and is selected from hydroxy and methoxy;

R² is difluoromethyl;

10 q is 0;

r is 0, or r is 1 or 2 and each R⁴ group is methyl, or r is 2 and the two R⁴ groups together form a methylene or ethylene group;

s is 2 and t is 2, or s is 1 and t is 3;

X¹ is CONH or CON(Me); and

15 Q¹ is methyl, ethyl, propyl, isopropyl, hydroxymethyl, 2-hydroxyethyl, 2-hydroxy-2-methylethyl, 1-hydroxy-1-methylethyl, 1-hydroxy-1-trifluoromethylethyl, methoxymethyl, 2-methoxyethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, methylsulphonylmethyl, 2-methylsulphonylethyl, methoxycarbonylmethyl, *tert*-butoxycarbonylmethyl, N-methylcarbamoylmethyl, N-ethylcarbamoylmethyl, 20 N-isopropylcarbamoylmethyl, N,N-dimethylcarbamoylmethyl, 2-(N,N-dimethylcarbamoyl)ethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-hydroxycycloprop-1-yl, tetrahydrofuran-3-yl, tetrahydropyran-4-yl, morpholin-2-yl, morpholin-3-yl, tetrahydro-1,4-thiazin-3-yl, azetidin-2-yl, pyrrolidin-2-yl, 5-aminopyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, N-methylpiperidin-3-yl, piperidin-4-yl, 25 N-methylpiperidin-4-yl, piperazin-1-yl, 4-methylpiperazin-1-yl, 2-oxo-1,3-thiazolidin-4-yl, 6-oxo-1,4,5,6-tetrahydropyridazin-3-yl, tetrahydrofuran-2-ylmethyl, tetrahydrofuran-3-ylmethyl, tetrahydropyran-4-ylmethyl, pyrrolidin-2-ylmethyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl, piperazin-1-ylmethyl, 2-oxo-1,3-oxazolidin-3-ylmethyl, 2-oxo-1,2-dihydropyridin-1-ylmethyl, phenyl, 30 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-carbamoylphenyl, 3-aminomethylphenyl, 4-aminomethylphenyl, benzyl, 2-aminobenzyl, 3-aminobenzyl, 4-aminobenzyl, 3-hydroxybenzyl, 4-mesylbenzyl, 1-formamido-1-phenylethyl, 2-phenylethyl, 3-phenylpropyl,

- 3-(4-methoxyphenyl)propyl, 1-hydroxy-3-phenylpropyl, 2-furyl, 3-furyl, 3-methylfuran-2-yl,
5-methylfuran-3-yl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 2-imidazolyl, *N*-methylimidazol-2-yl,
3-pyrazolyl, 1-methyl-1*H*-pyrazol-3-yl, 4-pyrazolyl, 2-oxazolyl, 4-oxazolyl,
2-methyloxazol-4-yl, 5-oxazolyl, 3-isoxazolyl, 5-methylisoxazol-3-yl, 4-isoxazolyl,
5 3-methylisoxazol-4-yl, 5-methylisoxazol-4-yl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl,
5-thiazolyl, 4-methylthiazol-5-yl, 1*H*-1,2,3-triazol-5-yl, 4*H*-1,2,4-triazol-3-yl,
3-amino-1*H*-1,2,4-triazol-5-yl, 5-hydroxy-4*H*-1,2,4-triazol-3-yl, 1,2,3-thiadiazol-4-yl,
2,1,3-thiadiazol-4-yl, 5-tetrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 4-pyridazinyl, 2-pyrazinyl,
3-aminopyrazin-2-yl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl,
10 2-hydroxy-4-methylpyrimidin-5-yl, 3-thienylmethyl, 2-imidazolylmethyl, 4-imidazolylmethyl,
5-methyl-1*H*-imidazol-4-ylmethyl, 1*H*-pyrazol-1-ylmethyl, 1*H*-pyrazol-3-ylmethyl,
3,5-dimethyl-1*H*-pyrazol-1-ylmethyl, 4-oxazolylmethyl, 3-isoxazolylmethyl,
5-methylisoxazol-3-ylmethyl, 5-isoxazolylmethyl, 1*H*-1,2,4-triazol-1-ylmethyl,
1*H*-tetrazol-1-ylmethyl, 1*H*-tetrazol-5-ylmethyl, 2-(1*H*-pyrazol-1-yl)ethyl,
15 2-(3-methyl-1*H*-pyrazol-1-yl)ethyl, 2-(1*H*-1,2,4-triazol-1-yl)ethyl, 2-pyridylmethyl,
3-pyridylmethyl, 4-pyridylmethyl, 4-pyridazinylmethyl, 4-pyrimidinylmethyl,
2-pyrazinylmethyl, 2-pyridin-3-ylethyl, 2-pyrimidin-4-ylethyl or 2-pyridazin-4-ylethyl;
and the 5-position on the pyrimidine ring is unsubstituted;
or a pharmaceutically-acceptable salt thereof.
- 20 A further particular compound of the invention is a pyrimidine derivative of the
Formula I wherein :-
- p is 0 or p is 1 and the R¹ group is located at the 4-position on the benzimidazolyl group
and is selected from hydroxy and methoxy;
- R² is difluoromethyl;
- 25 q is 0;
- r is 0, or r is 1 or 2 and each R⁴ group is methyl, or r is 2 and the two R⁴ groups together
form a methylene or ethylene group;
- s is 2 and t is 2, or s is 1 and t is 3;
- X¹ is CO; and
- 30 Q¹ is methyl, ethyl, isopropyl, hydroxymethyl, 2-hydroxy-2-methylethyl,
methoxymethyl, cyclopropyl, 1-hydroxycycloprop-1-yl, tetrahydropyran-4-yl, azetidin-1-yl,
azetidin-2-yl, pyrrolidin-1-yl, 3-dimethylaminopyrrolidin-1-yl, 2-carbamoylpyrrolidin-1-yl,

2-(2-methoxyethyl)pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, morpholin-2-yl,
morpholin-3-yl, tetrahydro-1,4-thiazin-4-yl, tetrahydro-1,4-thiazin-3-yl, piperidino,
4-aminopiperidino, 3-fluoropiperidino, 4-fluoropiperidino, 3-cyanomethylpiperidino,
piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, 3-oxopiperazin-1-yl,
5 tetrahydropyran-4-ylmethyl, pyrrolidin-2-ylmethyl, piperidin-3-ylmethyl,
piperazin-1-ylmethyl, phenyl, 3-carbamoylphenyl, 3-aminomethylphenyl,
4-aminomethylphenyl, 3-hydroxybenzyl, 2-furyl, 2-thienyl, 2-pyrrolyl, *N*-methylimidazol-2-yl,
3-pyrazolyl, 1-methyl-1*H*-pyrazol-3-yl, 4-pyrazolyl, 2-methyloxazol-4-yl, 5-isoxazolyl,
1*H*-1,2,3-triazol-5-yl, 1,2,3-thiadiazol-4-yl, 3-pyridyl, 4-pyridazinyl, 3-thienylmethyl,
10 1*H*-1,2,4-triazol-1-ylmethyl, 1*H*-tetrazol-1-ylmethyl, 1*H*-tetrazol-5-ylmethyl,
2-pyridin-3-ylethyl or 2-pyridazin-4-ylethyl;

and the 5-position on the pyrimidine ring is unsubstituted;
or a pharmaceutically-acceptable salt thereof.

A further particular compound of the invention is a pyrimidine derivative of the

15 Formula I wherein :-

p is 0 or p is 1 and the R¹ group is located at the 4-position on the benzimidazolyl group
and is selected from hydroxy and methoxy;

R² is difluoromethyl;

q is 0;

20 r is 0, or r is 1 or 2 and each R⁴ group is methyl;

s is 2 and t is 2, or s is 1 and t is 3;

X¹ is CONH or CON(Me); and

Q¹ is methyl, ethyl, isopropyl, allyl, hydroxymethyl, 2-hydroxy-2-methylethyl,
methoxymethyl, 4-aminobutyl, *N*-isopropylcarbamoylmethyl, cyclopropyl,

25 1-hydroxycycloprop-1-yl, cyclopropylmethyl, tetrahydropyran-4-yl, morpholin-2-yl,
morpholin-3-yl, tetrahydro-1,4-thiazin-3-yl, azetidin-2-yl, pyrrolidin-2-yl, piperidin-3-yl,
piperidin-4-yl, piperazin-1-yl, tetrahydrofuran-2-ylmethyl, tetrahydropyran-4-ylmethyl,
pyrrolidin-2-ylmethyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl, piperazin-1-ylmethyl,
phenyl, 3-carbamoylphenyl, 3-aminomethylphenyl, 4-aminomethylphenyl, 2-aminobenzyl,

30 3-aminobenzyl, 4-aminobenzyl, 3-hydroxybenzyl, 2-furyl, 2-thienyl, 2-pyrrolyl,
N-methylimidazol-2-yl, 3-pyrazolyl, 1-methyl-1*H*-pyrazol-3-yl, 4-pyrazolyl,
2-methyloxazol-4-yl, 5-isoxazolyl, 1*H*-1,2,3-triazol-5-yl, 1,2,3-thiadiazol-4-yl, 3-pyridyl,

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4-pyridazinyl, 3-thienylmethyl; 5-methylisoxazol-3-ylmethyl, 1*H*-1,2,4-triazol-1-ylmethyl, 1*H*-tetrazol-1-ylmethyl, 1*H*-tetrazol-5-ylmethyl, 4-pyridylmethyl, 2-pyridin-3-ylethyl, 2-pyridazin-4-ylethyl, 2-tolyloxymethyl or piperidin-4-yloxymethyl;

and the 5-position on the pyrimidine ring is unsubstituted;

5 or a pharmaceutically-acceptable salt thereof.

A further particular compound of the invention is a pyrimidine derivative of the Formula I wherein :-

p is 0 or p is 1 and the R¹ group is located at the 4-position on the benzimidazolyl group and is selected from hydroxy and methoxy;

10 R² is difluoromethyl;

q is 0;

r is 0, or r is 1 or 2 and each R⁴ group is methyl;

s is 2 and t is 2, or s is 1 and t is 3;

X¹ is CO; and

15 Q¹ is pyrrolidin-1-yl, 3-dimethylaminopyrrolidin-1-yl, 2-carbamoylpyrrolidin-1-yl, morpholino, tetrahydro-1,4-thiazin-4-yl, piperidino, 4-aminopiperidino, 4-fluoropiperidino, 3-cyanomethylpiperidino, piperazin-1-yl or 3-oxopiperazin-1-yl;

and the 5-position on the pyrimidine ring is unsubstituted;

or a pharmaceutically-acceptable salt thereof.

20 A further particular compound of the invention is a pyrimidine derivative of the Formula I wherein :-

p is 0 or p is 1 and the R¹ group is located at the 4-position on the benzimidazolyl group and is selected from hydroxy and methoxy;

R² is difluoromethyl;

25 q is 0;

r is 0, or r is 1 or 2 and each R⁴ group is methyl;

s is 2;

t is 2;

X¹ is CONH; and

30 Q¹ is methyl, ethyl, allyl, 4-aminobutyl, N-isopropylcarbamoylmethyl, 2-aminobenzyl, 3-aminobenzyl, 4-aminobenzyl, cyclopropylmethyl, 5-methylisoxazol-3-ylmethyl, 4-pyridylmethyl, 2-pyridin-3-ylethyl, tetrahydrofuran-2-ylmethyl or piperidin-4-ylmethyl;

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and the 5-position on the pyrimidine ring is unsubstituted;
or a pharmaceutically-acceptable salt thereof.

A further particular compound of the invention is a pyrimidine derivative of the Formula I wherein :-

5 p is 0 or p is 1 and the R¹ group is located at the 4-position on the benzimidazolyl group
and is selected from hydroxy and methoxy;

R² is difluoromethyl;

q is 0;

r is 0, or r is 1 or 2 and each R⁴ group is methyl;

10 s is 2;

t is 2;

X¹ is CO; and

Q¹ is 3-dimethylaminopyrrolidin-1-yl, morpholino, piperidino, 4-aminopiperidino or
4-fluoropiperidino;

15 and the 5-position on the pyrimidine ring is unsubstituted;
or a pharmaceutically-acceptable salt thereof.

A further particular compound of the invention is a pyrimidine derivative of the Formula I wherein :-

p is 0;

20 R² is difluoromethyl;

q is 0;

r is 0;

s is 2 and t is 2;

X¹ is a direct bond; and

25 Q¹ is amino-(1-6C)alkyl (such as aminomethyl or 2-aminoethyl, especially 2-
aminoethyl),

and the 5-position on the pyrimidine ring is unsubstituted;
or a pharmaceutically-acceptable salt thereof.

A further particular compound of the invention is a pyrimidine derivative of the Formula I wherein :-

p is 0;

R² is difluoromethyl;

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q is 0 or q is 1 and the R³ group is methyl;

r is 0;

s is 2 and t is 2;

X¹ is NHCO; and

5 Q¹ is amino-(1-6C)alkyl, aryl-(1-6C)alkyl or heterocyclyl (such as aminomethyl, 2-aminoethyl, 2-phenylethyl, pyrrolidinyl or piperidinyl, especially aminomethyl, 2-phenylethyl, pyrrolidinyl or piperidinyl),

10 and wherein any CH or CH₂ group within the Q¹ group optionally bears on each said CH or CH₂ group a substituent selected from methylamino and dimethylamino (especially methylamino),

15 and wherein any aryl or heterocyclyl group within the Q¹ group optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, methoxy, methylamino and dimethylamino and any such aryl or heterocyclyl group within the Q¹ group optionally bears a substituent selected from hydroxymethyl, methoxymethyl, cyanomethyl, aminomethyl, methylaminomethyl and dimethylaminomethyl;

and the 5-position on the pyrimidine ring is unsubstituted;
or a pharmaceutically-acceptable salt thereof.

A particular compound of the invention is, for example, the pyrimidine derivative ;

20 4-(2-difluoromethylbenzimidazol-1-yl)-
2-{4-[N-(N-methylcarbamoylmethyl)carbamoyl]piperidin-1-yl}-6-morpholinopyrimidine
(described hereinafter as Compound No. 1); or a pharmaceutically-acceptable salt thereof.

25 Further particular compounds of the invention are, for example, a pyrimidine derivative of the Formula I that is disclosed hereinafter as Example 1, 2, 3, 4 or 5, or a pharmaceutically-acceptable salt thereof.

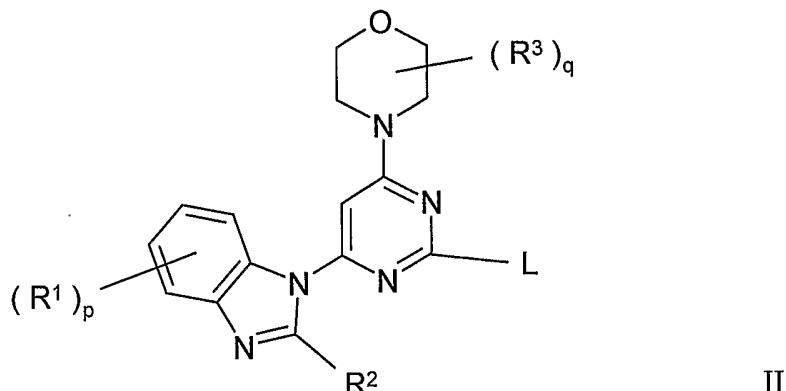
30 A pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a pyrimidine derivative of the Formula I are provided as a further feature of the invention and are illustrated by the following representative process variants in which, unless otherwise stated, p, R¹, R², q, R³, r, R⁴, s, t, X¹ and Q¹ have any of the meanings defined hereinbefore. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting

materials is described in conjunction with the following representative process variants.

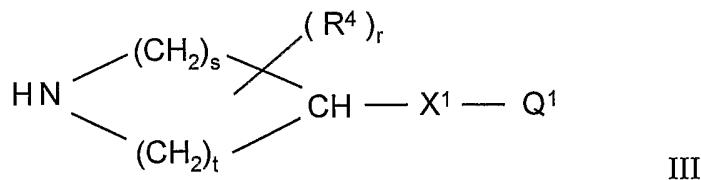
Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

(a) The reaction, conveniently in the presence of a suitable base, of a pyrimidine of the

5 Formula II



wherein L is a displaceable group as defined hereinafter and p, R¹, R², R³ and q have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted with a heterocyclic compound of the Formula III



10 wherein r, R⁴, s, t, X¹ and Q¹ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

A suitable displaceable group L is, for example, a halogeno, alkoxy, aryloxy or
15 sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, pentafluorophenoxy, methanesulphonyloxy or toluene-4-sulphonyloxy group.

Conveniently, the reaction may be carried out in the presence of a suitable base such as an alkali or alkaline earth metal carbonate or hydroxide, for example sodium bicarbonate, sodium carbonate, potassium bicarbonate, potassium carbonate, calcium carbonate, caesium carbonate, sodium hydroxide or potassium hydroxide, or, for example, an alkali metal alkoxide, for example sodium *tert*-butoxide, or, for example, an alkali metal amide, for
20

example sodium hexamethyldisilazane, or, for example, an alkali metal hydride, for example sodium hydride.

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an ether such as tetrahydrofuran, 1,4-dioxan or 1,2-dimethoxyethane, an aromatic solvent such as benzene, toluene or xylene, or an alcohol such as methanol or ethanol, or a dipolar aprotic solvent such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidin-2-one or dimethylsulphoxide, and the reaction is conveniently carried out at a temperature in the range, for example, 10 to 250°C, preferably in the range 40 to 120°C.

Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

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

A carboxy protecting group may be the residue of an ester-forming aliphatic or arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (for example isopropyl, and *tert*-butyl); lower alkoxy-lower alkyl groups (for example methoxymethyl, ethoxymethyl and isobutoxymethyl); lower acyloxy-lower alkyl groups, (for example acetoxyethyl, propionyloxymethyl, butyryloxymethyl and pivaloyloxymethyl); lower alkoxy carbonyloxy-lower alkyl groups (for example 1-methoxycarbonyloxyethyl and 1-ethoxycarbonyloxyethyl); aryl-lower alkyl groups (for example benzyl, 4-methoxybenzyl, 2-nitrobenzyl, 4-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for example trimethylsilyl and *tert*-butyldimethylsilyl); tri(lower alkyl)silyl-lower alkyl groups

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(for example trimethylsilyl ethyl); and (2-6C)alkenyl groups (for example allyl). Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed cleavage.

Examples of hydroxy protecting groups include lower alkyl groups (for example

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

Examples of amino protecting groups include formyl, aryl-lower alkyl groups (for

- example benzyl and substituted benzyl, 4-methoxybenzyl, 2-nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-4-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (for example *tert*-butoxycarbonyl); lower alkenyloxycarbonyl (for example allyloxycarbonyl); aryl-lower alkoxycarbonyl groups (for example benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl and 4-nitrobenzyloxycarbonyl); trialkylsilyl (for example trimethylsilyl and *tert*-butyldimethylsilyl); alkylidene (for example methylidene) and benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for

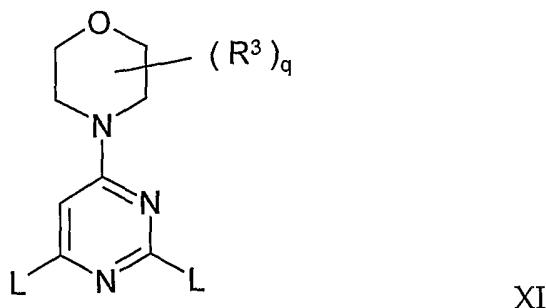
- 20 example, acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as 2-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as 2-nitrobenzyloxycarbonyl.

The reader is referred to Advanced Organic Chemistry, 4th Edition, by J. March,

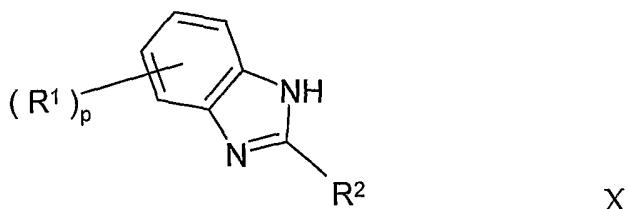
- 25 published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents and to Protective Groups in Organic Synthesis, 2nd Edition, by T. Green *et al.*, also published by John Wiley & Son, for general guidance on protecting groups.

Pyrimidine starting materials of the Formula II may be obtained by conventional procedures. For example, a pyrimidine of the Formula XI

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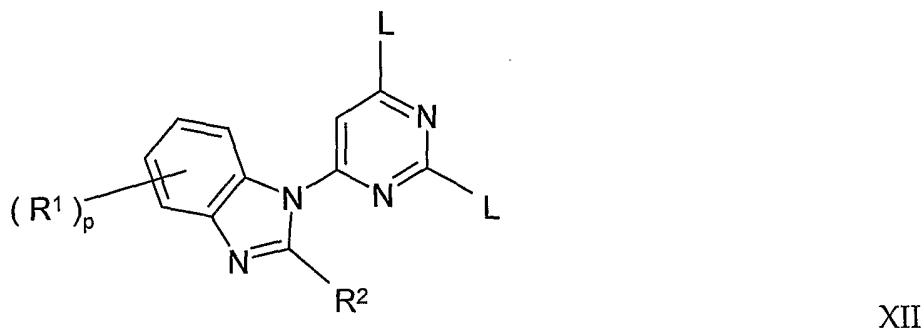


wherein L is a displaceable group as defined hereinbefore and q and R³ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted, conveniently in the presence of a suitable base as defined hereinbefore, with a benzimidazole of the Formula X

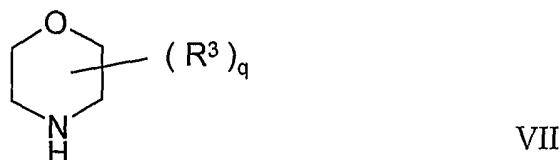


wherein p, R¹ and R² have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

10 Alternatively, a pyrimidine of the Formula XII



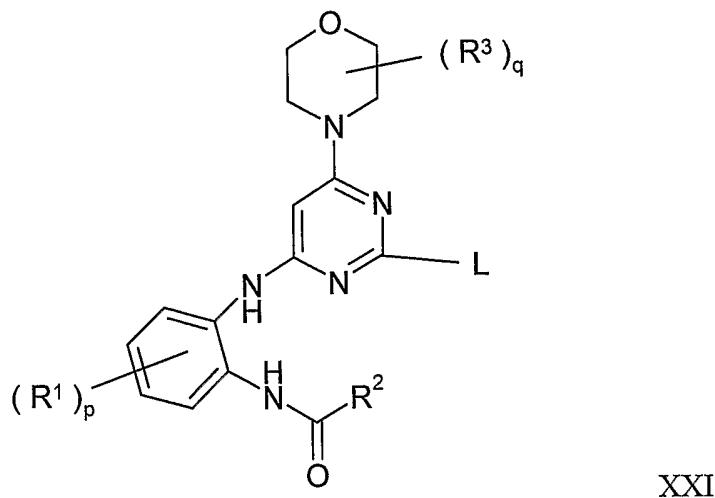
wherein L is a displaceable group as defined hereinbefore and p, R¹ and R² have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted with a morpholine of the Formula VII



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wherein q and R³ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

Alternatively, a pyrimidine of the Formula XXI

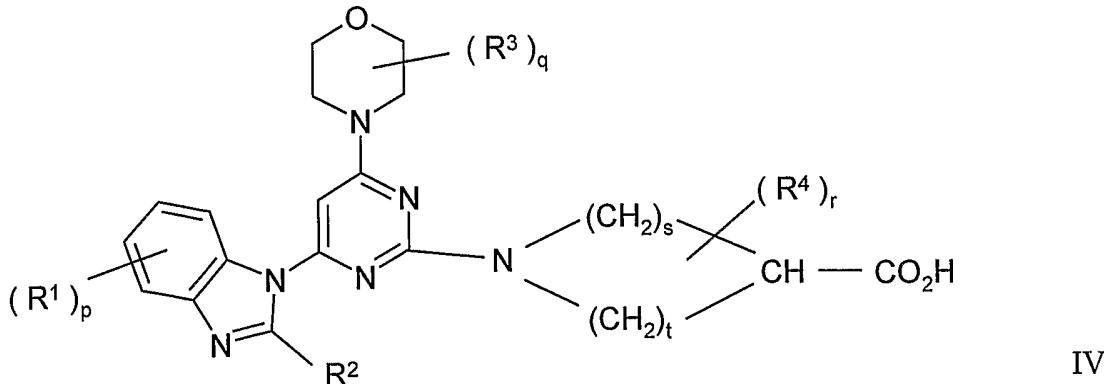


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wherein L is a displaceable group as defined hereinbefore and p, R¹, R², q and R³ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted under conditions suitable for affecting a ring closure reaction, for example by reaction with a suitable acid (such as hydrochloric acid or trifluoroacetic acid), whereafter any 10 protecting group that is present is removed by conventional means.

10

- (b) For the production of those compounds of the Formula I wherein X¹ is CON(R¹³), the coupling, conveniently in the presence of a suitable base, of a carboxylic acid of the Formula IV



15

- or a reactive derivative thereof as defined hereinafter, wherein p, R¹, R², q, R³, r, R⁴, s and t have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an amine of the Formula V



wherein R^{13} and Q^1 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

5 A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, diisopropylethylamine, *N*-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide,
10 or, for example, an alkali metal amide, for example sodium hexamethyldisilazane, or, for example, an alkali metal hydride, for example sodium hydride.

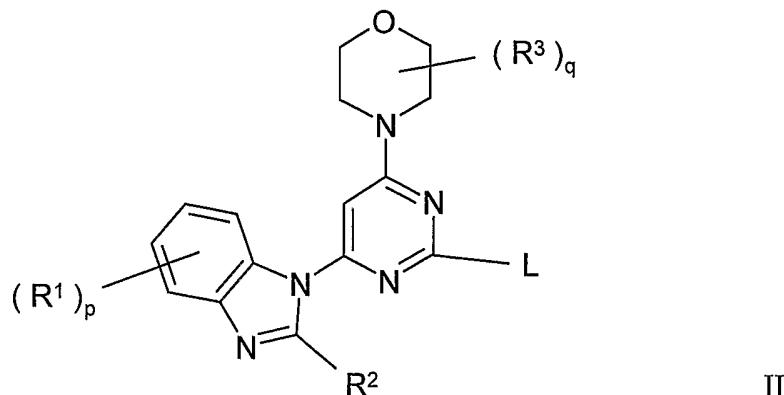
A suitable reactive derivative of a carboxylic acid of the Formula IV is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid with an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride
15 formed by the reaction of the acid with a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid with a phenol such as pentafluorophenol, with an ester such as pentafluorophenyl trifluoroacetate or with an alcohol such as methanol, ethanol, isopropanol, butanol or *N*-hydroxybenzotriazole; an acyl azide, for example an azide formed by the reaction of the acid with an azide such as diphenylphosphoryl
20 azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid with a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid with a carbodiimide such as dicyclohexylcarbodiimide or with a uronium compound such as 2-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate(V).

The reaction is conveniently carried out in the presence of a suitable inert solvent or
25 diluent, for example an alcohol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene.

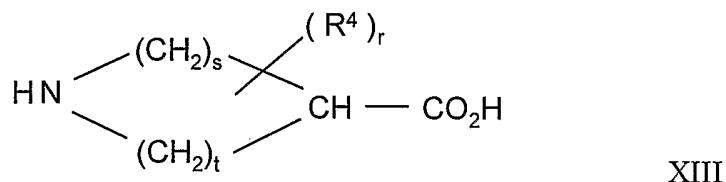
Conveniently, the reaction is carried out in the presence of a dipolar aprotic solvent such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidin-2-one or
30 dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, for example, 0 to 120°C, preferably at or near ambient temperature.

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Pyrimidine starting materials of the Formula IV may be obtained by conventional procedures. For example, a pyrimidine of the Formula II

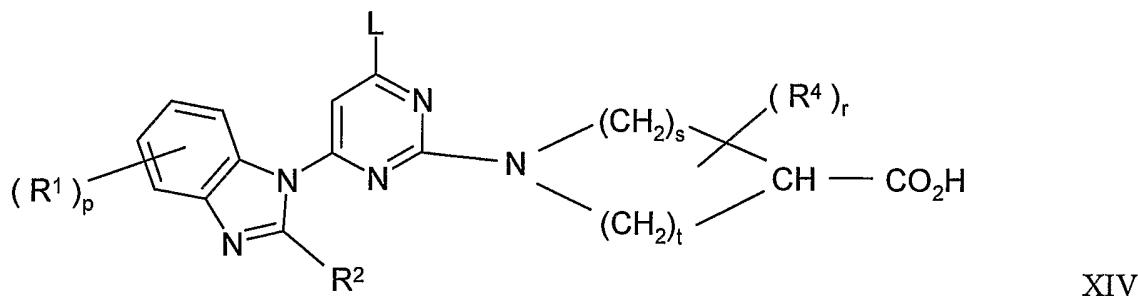


wherein L is a displaceable group as defined hereinbefore and p, R¹, R², R³ and q have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted with a heterocyclic compound of the Formula XIII



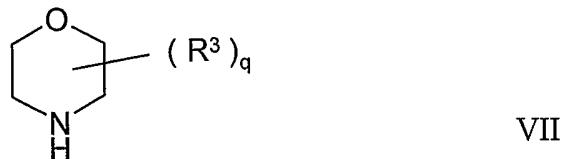
wherein r, R⁴, s and t have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

Alternatively, a pyrimidine of the Formula XIV



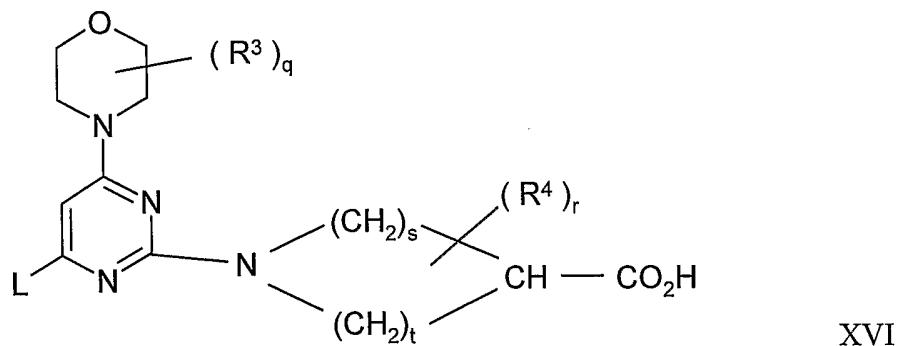
wherein L is a displaceable group as defined hereinbefore and p, R¹, R², r, R⁴, s and t have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted with a morpholine of the Formula VII

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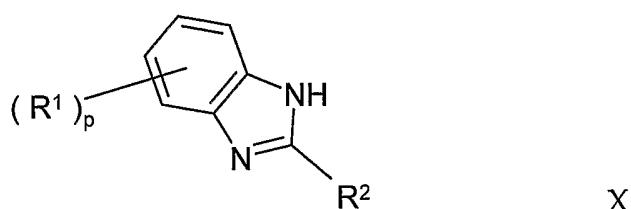


wherein q and R³ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

5 Alternatively, a pyrimidine of the Formula XVI



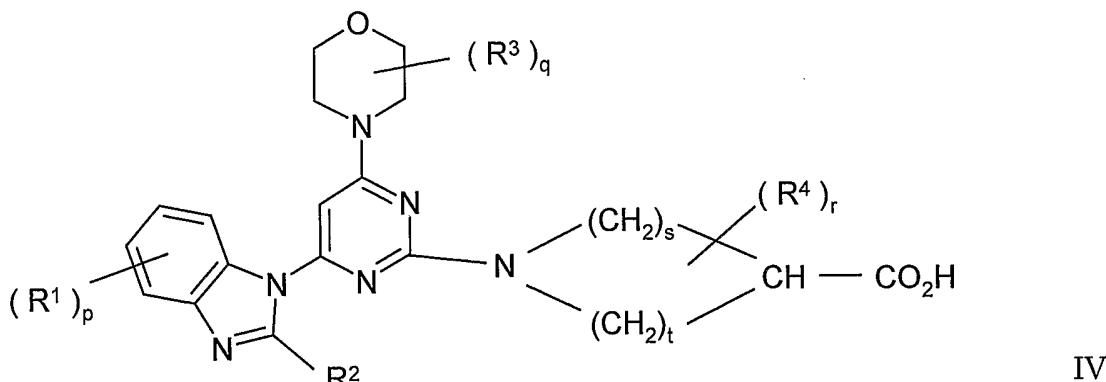
wherein L is a displaceable group as defined hereinbefore and q, R³, r, R⁴, s and t have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted, conveniently in the presence of a suitable base as defined hereinbefore, with a
10 benzimidazole of the Formula X



wherein p, R¹ and R² have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

15 (c) For the production of those compounds of the Formula I wherein X¹ is CO and Q¹ is a heterocyclil group that contains an NH group, the coupling, conveniently in the presence of a suitable base as defined hereinbefore, of the NH-containing heterocyclil group where any functional group (other than the reacting NH group) is protected if necessary with a carboxylic acid of the Formula IV

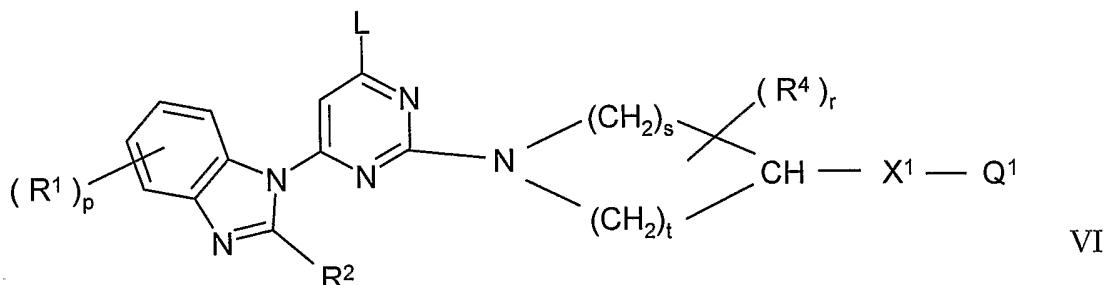
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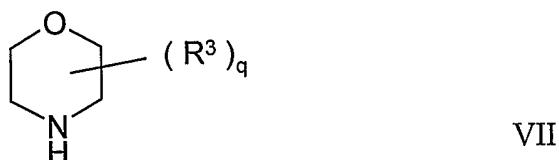
or a reactive derivative thereof as defined hereinbefore, wherein p, R¹, R², q, R³, r, R⁴, s and t have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

5 The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 0 to 120°C, preferably at or near ambient temperature.

(d) The reaction of a pyrimidine of the Formula VI



10 wherein L is a displaceable group as defined hereinbefore and p, R¹, R², r, R⁴, s, t, X¹ and Q¹ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a morpholine compound of the Formula VII



wherein q and R³ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

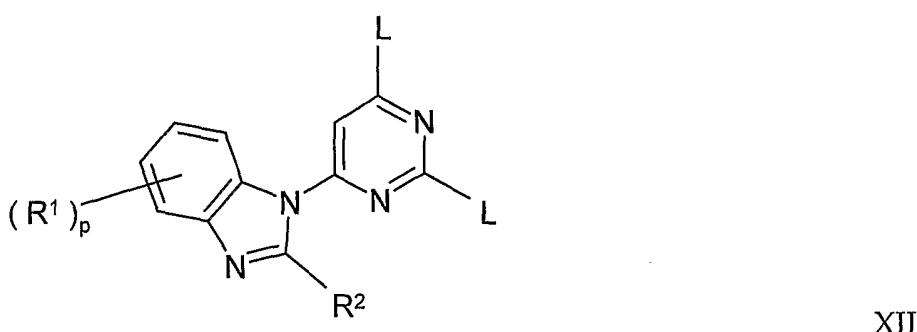
The reaction may conveniently be carried out in the presence of a suitable acid or in the presence of a suitable base. A suitable acid is, for example, an inorganic acid such as, for example, hydrogen chloride or hydrogen bromide. A suitable base is, for example, an organic

amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, *N*-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide,
5 or, for example, an alkali metal amide, for example sodium hexamethyldisilazane, or, for example, an alkali metal hydride, for example sodium hydride.

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an alcohol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride,
10 an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, for example, 0 to 250°C, preferably in the range 25 to 150°C.

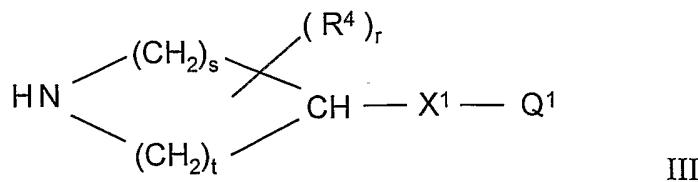
Typically, the pyrimidine of the Formula VI may be reacted with a morpholine of the
15 Formula VII in the presence of an aprotic solvent such as *N,N*-dimethylformamide or *N,N*-dimethylacetamide, conveniently in the presence of a suitable base, for example potassium carbonate or sodium hexamethyldisilazane, and at a temperature in the range, for example, 0 to 200°C, preferably in the range, for example, 25 to 150°C.

Pyrimidine starting materials of the Formula VI may be obtained by conventional
20 procedures. For example, a pyrimidine of the Formula XII



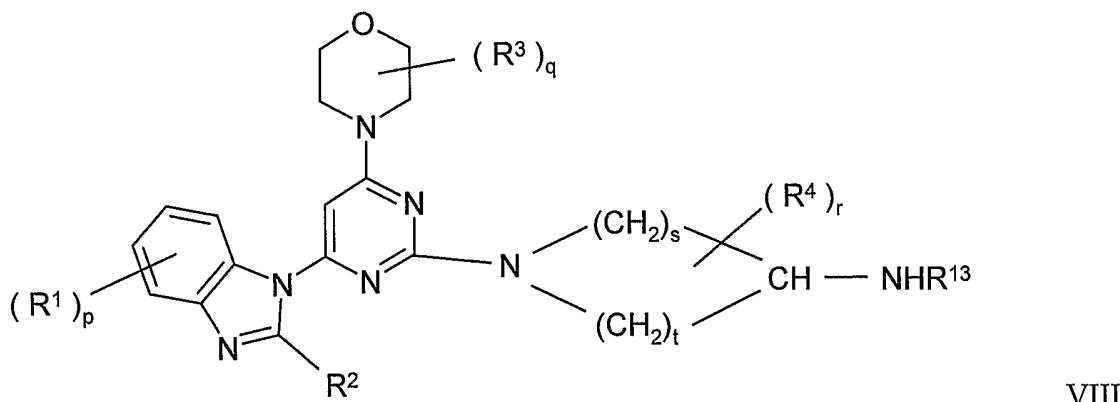
wherein L is a displaceable group as defined hereinbefore and p, R¹ and R² have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted with a heterocyclic compound of the Formula III

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wherein r, R⁴, s, t, X¹ and Q¹ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

- 5 (e) For the production of those compounds of the Formula I wherein X¹ is N(R¹³)CO and Q¹ is a heterocyclyl group that contains an NH group, the coupling, conveniently in the presence of a suitable base as defined hereinbefore, of phosgene, or a chemical equivalent thereof, with the NH-containing heterocyclyl group where any functional group (other than the reacting NH group) is protected if necessary and with a pyrimidine of the Formula VIII



- 10 wherein p, R¹, R², q, R³, r, R⁴, s, t and R¹³ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

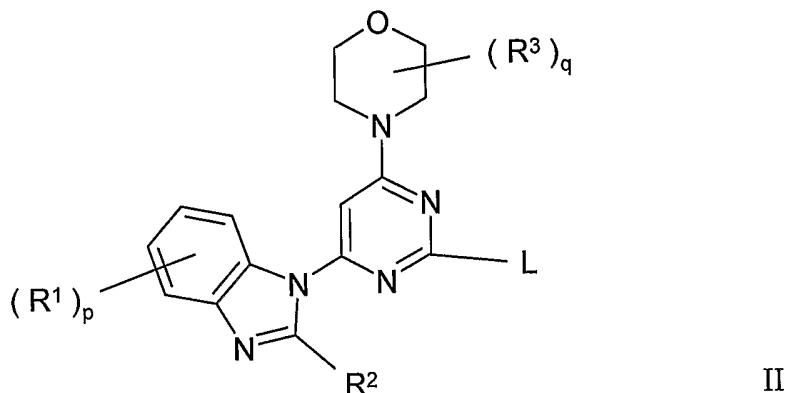
A suitable chemical equivalent of phosgene is, for example, a compound of the
15 Formula XIV



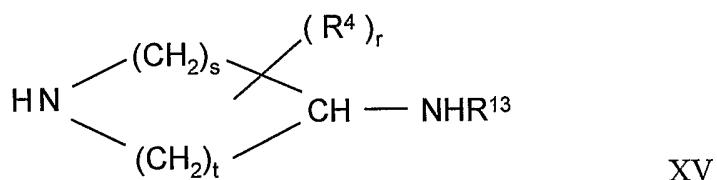
- wherein L is a suitable displaceable group as defined hereinbefore. For example, a suitable displaceable group L is, for example, an alkoxy, aryloxy or sulphonyloxy group, for example a methoxy, phenoxy, methanesulphonyloxy or toluene-4-sulphonyloxy group. Alternatively, a
20 suitable chemical equivalent of phosgene is a carbonate derivative such as disuccinimido carbonate.

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 0 to 120°C, preferably at or near ambient temperature.

Pyrimidine starting materials of the Formula VIII may be obtained by conventional procedures. For example, a pyrimidine of the Formula II

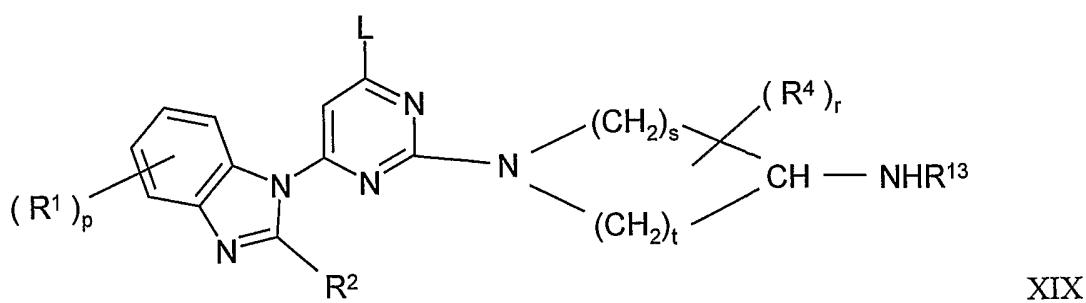


wherein L is a displaceable group as defined hereinbefore and p, R¹, R², R³ and q have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted with a heterocyclic ring of the Formula XV



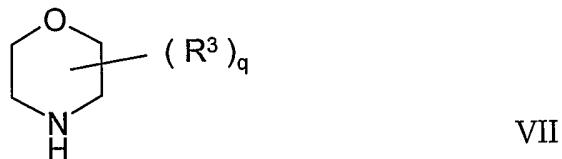
wherein r, R⁴, s, t and R¹³ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

Alternatively, a pyrimidine of the Formula XIX



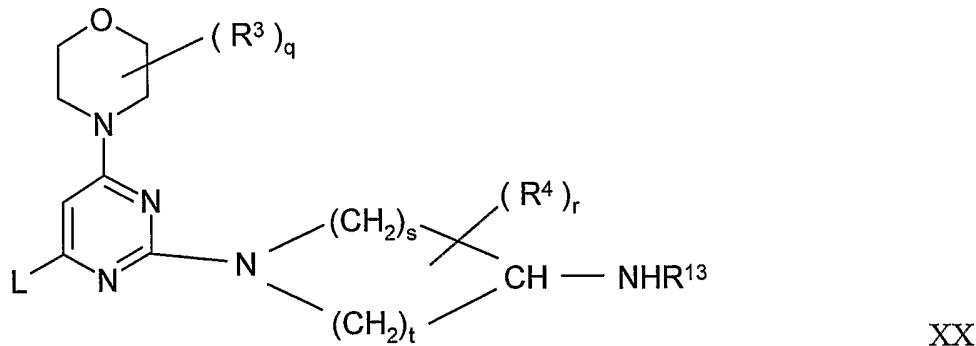
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wherein L is a displaceable group as defined hereinbefore and p, R¹, R², R⁴, r, s, t and R¹³ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted with a morpholine compound of the Formula VII

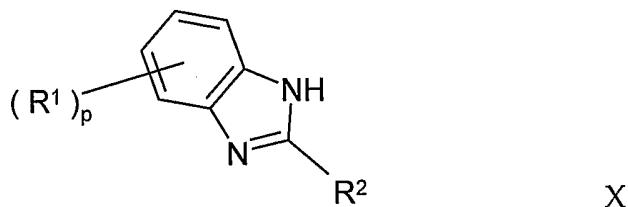


- 5 wherein q and R³ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

Alternatively, a pyrimidine of the Formula XX

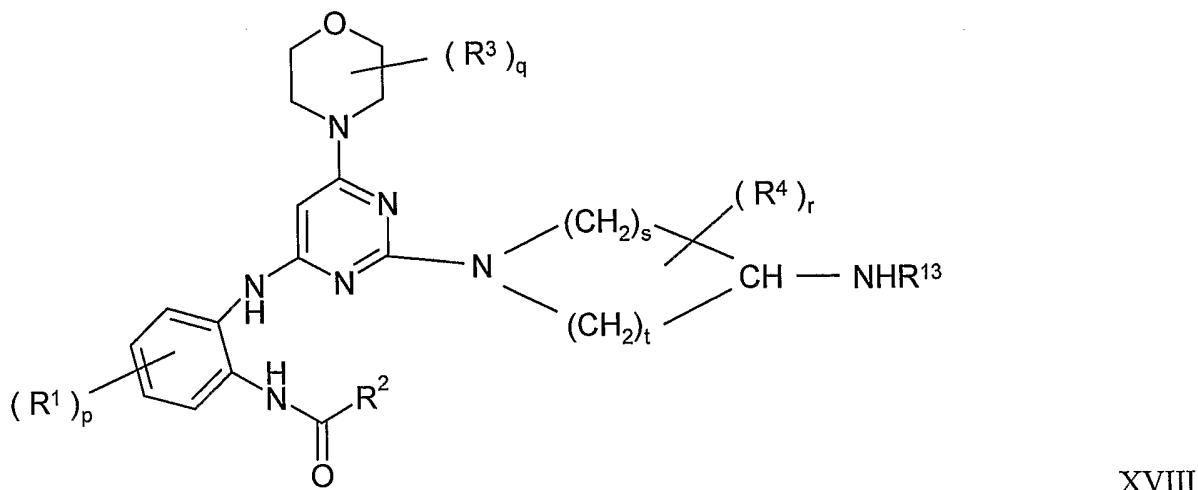


- 10 wherein L is a displaceable group as defined hereinbefore and q, R³, r, R⁴, s, t and R¹³ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted, conveniently in the presence of a suitable base as defined hereinbefore, with a benzimidazole of the Formula X



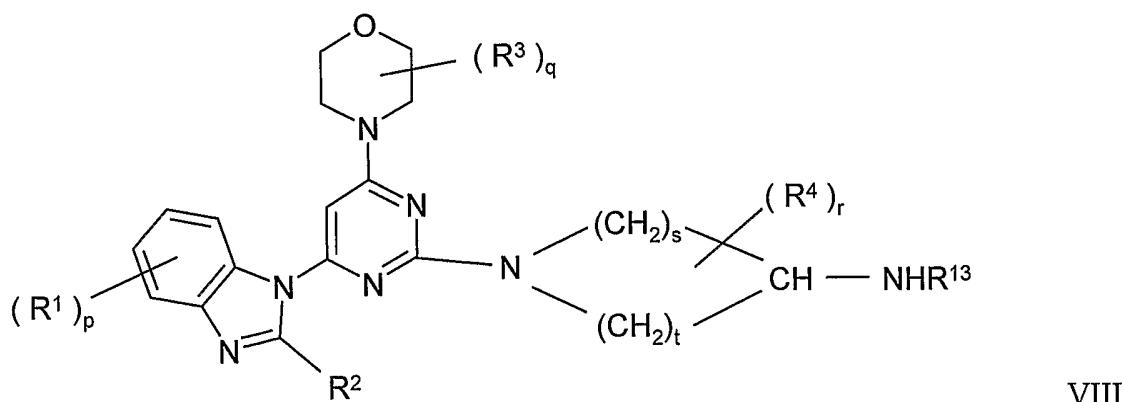
- 15 wherein p, R¹ and R² have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means. As the skilled person would appreciate, the free -NH group attached to the heterocyclic group of the pyrimidine of the Formula XX typically would be protected by a suitable protecting group prior to reaction with the benzimidazole of the Formula X.

Alternatively, a pyrimidine of the Formula XVIII



wherein p, R¹, R², q, R³, s, t, r, R⁴ and R¹³ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted under conditions suitable for affecting a ring closure reaction, for example by reaction with a suitable acid (such as hydrochloric acid or trifluoroacetic acid), whereafter any protecting group that is present is removed by conventional means.

(f) For the production of those compounds of the Formula I wherein X¹ is N(R¹³)CON(R¹³), the coupling, conveniently in the presence of a suitable base as defined hereinbefore, of phosgene, or a chemical equivalent thereof as defined hereinbefore, with a pyrimidine of the Formula VIII



wherein p, R¹, R², q, R³, r, R⁴, s, t and R¹³ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, and with an amine of the Formula V

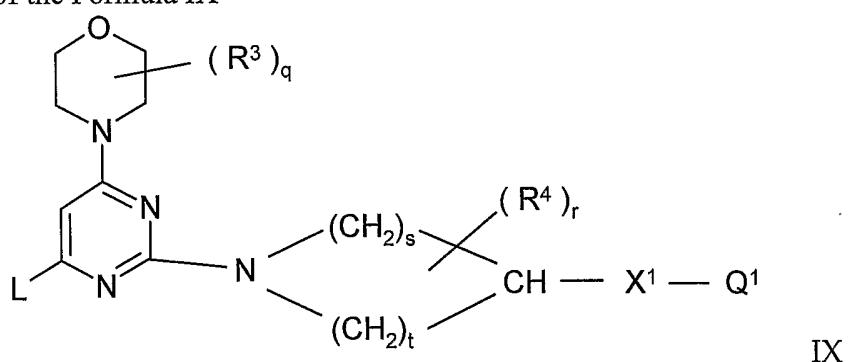


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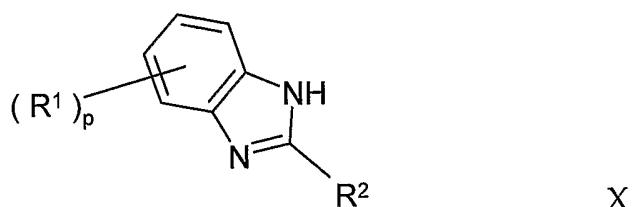
wherein R¹³ and Q¹ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 0 to 120°C, preferably at or near ambient temperature.

(g) The reaction, conveniently in the presence of a suitable base as defined hereinbefore, of a pyrimidine of the Formula IX



wherein L is a displaceable group as defined hereinbefore and q, R³, r, R⁴, s, t, X¹ and Q¹ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a benzimidazole of the Formula X



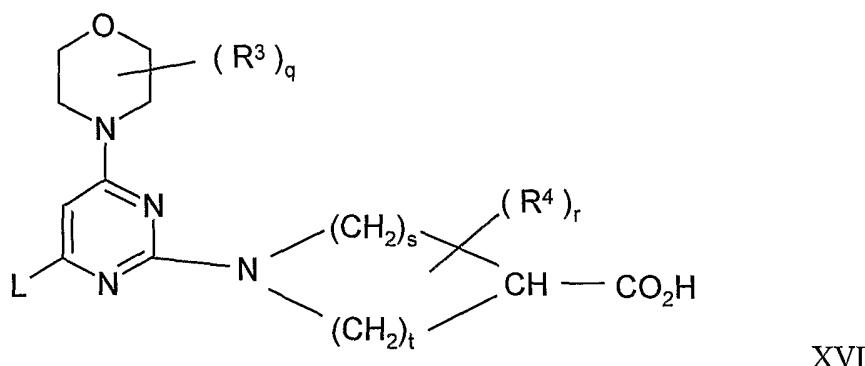
wherein p, R¹ and R² have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

Conveniently, the reaction may be carried out in the presence of a suitable base such as an alkali or alkaline earth metal carbonate or hydroxide, for example sodium bicarbonate, sodium carbonate, potassium bicarbonate, potassium carbonate, calcium carbonate, caesium carbonate, sodium hydroxide or potassium hydroxide, or, for example, an alkali metal alkoxide, for example sodium *tert*-butoxide, or, for example, an alkali metal amide, for example sodium hexamethyldisilazane, or, for example, an alkali metal hydride, for example sodium hydride.

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example an ether such as tetrahydrofuran, 1,4-dioxan or 1,2-dimethoxyethane, an aromatic solvent such as benzene, toluene or xylene, or an alcohol such as methanol or ethanol. Conveniently, the reaction is carried out in the presence of a dipolar aprotic solvent such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidin-2-one or dimethylsulphoxide. Conveniently, the reaction is carried out at a temperature in the range, for example 10 to 250°C, preferably in the range 40 to 150°C.

Pyrimidine starting materials of the Formula IX may be obtained by conventional procedures.

For example, for the production of those compounds of the Formula IX wherein X¹ is CON(R¹³), a carboxylic acid of the Formula XVI



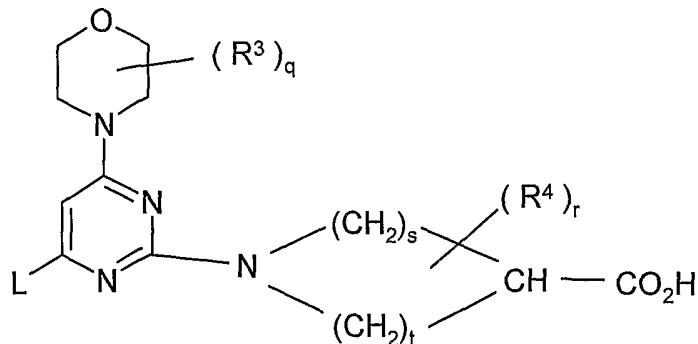
or a reactive derivative thereof as defined hereinbefore, wherein L is a displaceable group as defined hereinbefore and q, R³, r, R⁴, s and t have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be coupled, conveniently in the presence of a suitable base as defined hereinbefore, with an amine of the Formula V



wherein R¹³ and Q¹ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

For example, for the production of those compounds of the Formula IX wherein X¹ is CO and Q¹ is a heterocyclyl group that contains an NH group, a carboxylic acid of the Formula XVI

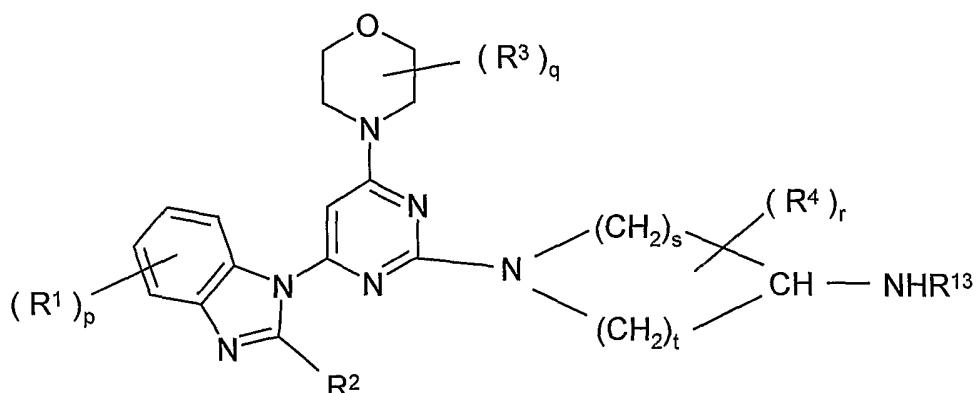
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XVI

or a reactive derivative thereof as defined hereinbefore, wherein L is a displaceable group as defined hereinbefore and q, R³, r, R⁴, s and t have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be coupled, conveniently in the presence of a suitable base as defined hereinbefore, with the NH-containing heterocyclyl group Q¹ where any functional group (other than the reacting NH group) is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

(h) For the production of those compounds of the Formula I wherein X¹ is N(R¹³)CO or N(R¹³)COC(R¹³)₂N(R¹³)CO, the coupling, conveniently in the presence of a suitable base, of a pyrimidine of the Formula VIII



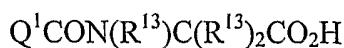
VIII

wherein p, R¹, R², q, R³, r, R⁴, s, t and R¹³ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a carboxylic acid of the formula XVII or XVII'

15



XVII



XVII'

or a reactive derivative thereof, wherein Q¹ and R¹³ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any

protecting group that is present is removed by conventional means. Suitable bases and reaction conditions are for example as defined hereinbefore in relation to process (b).

The pyrimidine derivative of the Formula I may be obtained from the process variants described hereinbefore in the form of the free base or alternatively it may be obtained in the 5 form of a salt with the acid of the formula H-L wherein L has the meaning defined hereinbefore. When it is desired to obtain the free base from the salt, the salt may be treated with a suitable base, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline 10 earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide.

When a pharmaceutically-acceptable salt of a pyrimidine derivative of the Formula I is required, for example an acid-addition salt, it may be obtained by, for example, reaction of said pyrimidine derivative with a suitable acid using a conventional procedure.

15 When a pharmaceutically-acceptable pro-drug of a pyrimidine derivative of the Formula I is required, it may be obtained using a conventional procedure. For example, an *in vivo* cleavable ester of a pyrimidine derivative of the Formula I may be obtained by, for example, reaction of a compound of the Formula I containing a carboxy group with a pharmaceutically-acceptable alcohol or by reaction of a compound of the Formula I containing 20 a hydroxy group with a pharmaceutically-acceptable carboxylic acid. For example, an *in vivo* cleavable amide of a pyrimidine derivative of the Formula I may be obtained by, for example, reaction of a compound of the Formula I containing a carboxy group with a pharmaceutically-acceptable amine or by reaction of a compound of the Formula I containing an amino group with a pharmaceutically-acceptable carboxylic acid.

25 Many of the intermediates defined herein are novel and these are provided as a further feature of the invention. For example, many compounds of the Formulae IV, VI, VIII and IX are novel compounds.

Biological Assays

The following assays can be used to measure the effects of the compounds of the present 30 invention as PI3 kinase inhibitors, as mTOR PI kinase-related kinase inhibitors, as inhibitors *in vitro* of the activation of PI3 kinase signalling pathways, as inhibitors *in vitro* of the activation of PI3 kinase signalling pathways, as inhibitors *in vitro* of the proliferation of MDA-MB-468

human breast adenocarcinoma cells, and as inhibitors *in vivo* of the growth in nude mice of xenografts of MDA-MB-468 carcinoma tissue.

(a) In Vitro PI3K Enzyme Assay

The assay used AlphaScreen technology (Gray *et al.*, Analytical Biochemistry, 2003, 5 313: 234-245) to determine the ability of test compounds to inhibit phosphorylation by recombinant Type I PI3K enzymes of the lipid PI(4,5)P₂.

DNA fragments encoding human PI3K catalytic and regulatory subunits were isolated from cDNA libraries using standard molecular biology and PCR cloning techniques. The selected DNA fragments were used to generate baculovirus expression vectors. In particular, 10 full length DNA of each of the p110 α , p110 β and p110 δ Type Ia human PI3K p110 isoforms (EMBL Accession Nos. HSU79143, S67334, Y10055 for p110 α , p110 β and p110 δ respectively) were sub-cloned into a pDEST10 vector (Invitrogen Limited, Fountain Drive, Paisley, UK). The vector is a Gateway-adapted version of Fastbac1 containing a 6-His epitope tag. A truncated form of Type Ib human PI3K p110 γ isoform corresponding to amino acid 15 residues 144-1102 (EMBL Accession No. X8336A) and the full length human p85 α regulatory subunit (EMBL Accession No. HSP13KIN) were also sub-cloned into pFastBac1 vector containing a 6-His epitope tag. The Type Ia p110 constructs were co-expressed with the p85 α regulatory subunit. Following expression in the baculovirus system using standard baculovirus expression techniques, expressed proteins were purified using the His epitope tag 20 using standard purification techniques.

DNA corresponding to amino acids 263 to 380 of human general receptor for phosphoinositides (Grp1) PH domain was isolated from a cDNA library using standard molecular biology and PCR cloning techniques. The resultant DNA fragment was sub-cloned 25 into a pGEX 4T1 *E. coli* expression vector containing a GST epitope tag (Amersham Pharmacia Biotech, Rainham, Essex, UK) as described by Gray *et al.*, Analytical Biochemistry, 2003, 313: 234-245). The GST-tagged Grp1 PH domain was expressed and purified using standard techniques.

Test compounds were prepared as 10 mM stock solutions in DMSO and diluted into water as required to give a range of final assay concentrations. Aliquots (2 μ l) of each 30 compound dilution were placed into a well of a Greiner 384-well low volume (LV) white polystyrene plate (Greiner Bio-one, Brunel Way, Stonehouse, Gloucestershire, UK Catalogue No. 784075). A mixture of each selected recombinant purified PI3K enzyme (15 ng),

DiC8-PI(4,5)P2 substrate (40 μ M; Cell Signals Inc., Kinnear Road, Columbus, USA, Catalogue No. 901), adenosine triphosphate (ATP; 4 μ M) and a buffer solution [comprising Tris-HCl pH7.6 buffer (40 mM, 10 μ l), 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulphonate (CHAPS; 0.04%), dithiothreitol (DTT; 2 mM) and magnesium chloride (10 mM)] was agitated at room temperature for 20 minutes.

Control wells that produced a minimum signal corresponding to maximum enzyme activity were created by using 5% DMSO instead of test compound. Control wells that produced a maximum signal corresponding to fully inhibited enzyme were created by adding wortmannin (6 μ M; Calbiochem / Merck Bioscience, Padge Road, Beeston, Nottingham, UK, Catalogue No. 681675) instead of test compound. These assay solutions were also agitated for 20 minutes at room temperature.

Each reaction was stopped by the addition of 10 μ l of a mixture of EDTA (100 mM), bovine serum albumin (BSA, 0.045 %) and Tris-HCl pH7.6 buffer (40 mM).

Biotinylated-DiC8-PI(3,4,5)P3 (50 nM; Cell Signals Inc., Catalogue No. 107), recombinant purified GST-Grp1 PH protein (2.5 nM) and AlphaScreen Anti-GST donor and acceptor beads (100 ng; Packard Bioscience Limited, Station Road, Pangbourne, Berkshire, UK, Catalogue No. 6760603M) were added and the assay plates were left for about 5 to 20 hours at room temperature in the dark. The resultant signals arising from laser light excitation at 680 nm were read using a Packard AlphaQuest instrument.

PI(3,4,5)P3 is formed *in situ* as a result of PI3K mediated phosphorylation of PI(4,5)P2. The GST-Grp1 PH domain protein that is associated with AlphaScreen Anti-GST donor beads forms a complex with the biotinylated PI(3,4,5)P3 that is associated with Alphascreen Streptavidin acceptor beads. The enzymatically-produced PI(3,4,5)P3 competes with biotinylated PI(3,4,5)P3 for binding to the PH domain protein. Upon laser light excitation at 680 nm, the donor bead : acceptor bead complex produces a signal that can be measured. Accordingly, PI3K enzme activity to form PI(3,4,5)P3 and subsequent competition with biotinylated PI(3,4,5)P3 results in a reduced signal. In the presence of a PI3K enzyme inhibitor, signal strength is recovered.

PI3K enzyme inhibition for a given test compound was expressed as an IC₅₀ value.

Thereby, the inhibitory properties of compounds of formula (I) against PI3K enzymes, such as the Class Ia PI3K enzymes (*e.g.* PI3Kalpha, PI3Kbeta and PI3Kdelta) and the Class Ib PI3K enzyme (PI3Kgamma) may be demonstrated.

(b) In Vitro mTOR PI kinase-related Kinase Assay

The assay used AlphaScreen technology (Gray *et al.*, Analytical Biochemistry, 2003, 313: 234-245) to determine the ability of test compounds to inhibit phosphorylation by recombinant mTOR.

A C-terminal truncation of mTOR encompassing amino acid residues 1362 to 2549 of mTOR (EMBL Accession No. L34075) was stably expressed as a FLAG-tagged fusion in HEK293 cells as described by Vilella-Bach *et al.*, Journal of Biochemistry, 1999, 274, 4266-4272. The HEK293 FLAG-tagged mTOR (1362-2549) stable cell line was routinely maintained at 37°C with 5% CO₂ up to a confluence of 70-90% in Dulbecco's modified Eagle's growth medium (DMEM; Invitrogen Limited, Paisley, UK Catalogue No. 41966-029) containing 10% heat-inactivated foetal calf serum (FCS; Sigma, Poole, Dorset, UK, Catalogue No. F0392), 1% L-glutamine (Gibco, Catalogue No. 25030-024) and 2 mg/ml Geneticin (G418 sulphate; Invitrogen Limited, UK Catalogue No. 10131-027). Following expression in the mammalian HEK293 cell line, expressed protein was purified using the FLAG epitope tag using standard purification techniques.

Test compounds were prepared as 10 mM stock solutions in DMSO and diluted into water as required to give a range of final assay concentrations. Aliquots (2 µl) of each compound dilution were placed into a well of a Greiner 384-well low volume (LV) white polystyrene plate (Greiner Bio-one). A 30 µl mixture of recombinant purified mTOR enzyme, 1 µM biotinylated peptide substrate (Biotin-Ahx-Lys-Lys-Ala-Asn-Gln-Val-Phe-Leu-Gly-Phe-Thr-Tyr-Val-Ala-Pro-Ser-Val-Leu-Glu-Ser-Val-Lys-Glu-NH₂; Bachem UK Ltd), ATP (20 µM) and a buffer solution [comprising Tris-HCl pH7.4 buffer (50 mM), EGTA (0.1 mM), bovine serum albumin (0.5 mg/ml), DTT (1.25 mM) and manganese chloride (10 mM)] was agitated at room temperature for 90 minutes.

Control wells that produced a maximum signal corresponding to maximum enzyme activity were created by using 5% DMSO instead of test compound. Control wells that produced a minimum signal corresponding to fully inhibited enzyme were created by adding EDTA (83 mM) instead of test compound. These assay solutions were incubated for 2 hours at room temperature.

Each reaction was stopped by the addition of 10 µl of a mixture of EDTA (50 mM), bovine serum albumin (BSA; 0.5 mg/ml) and Tris-HCl pH7.4 buffer (50 mM) containing p70 S6 Kinase (T389) 1A5 Monoclonal Antibody (Cell Signalling Technology, Catalogue

No. 9206B) and AlphaScreen Streptavidin donor and Protein A acceptor beads (200 ng; Perkin Elmer, Catalogue No. 6760002B and 6760137R respectively) were added and the assay plates were left for about 20 hours at room temperature in the dark. The resultant signals arising from laser light excitation at 680 nm were read using a Packard Envision instrument.

5 Phosphorylated biotinylated peptide is formed *in situ* as a result of mTOR mediated phosphorylation. The phosphorylated biotinylated peptide that is associated with AlphaScreen Streptavidin donor beads forms a complex with the p70 S6 Kinase (T389) 1A5 Monoclonal Antibody that is associated with Alphascreen Protein A acceptor beads. Upon laser light excitation at 680 nm, the donor bead : acceptor bead complex produces a signal that can be measured. Accordingly, the presence of mTOR kinase activity results in an assay signal. In 10 the presence of an mTOR kinase inhibitor, signal strength is reduced.

mTOR enzyme inhibition for a given test compound was expressed as an IC₅₀ value.

(c) In Vitro phospho-Ser473 Akt assay

15 This assay determines the ability of test compounds to inhibit phosphorylation of Serine 473 in Akt as assessed using Acumen Explorer technology (TTP LabTech Limited, Royston, Herts, SG8 6EE, UK), a plate reader that can be used to rapidly quantitate features of 20 images generated by laser-scanning.

A MDA-MB-468 human breast adenocarcinoma cell line (LGC Promochem, Teddington, Middlesex, UK, Catalogue No. HTB-132) was routinely maintained at 37°C with 5% CO₂ up to a confluence of 70–90% in DMEM containing 10% FCS and 1% L-glutamine.

25 For the assay, the cells were detached from the culture flask using ‘Accutase’ (Innovative Cell Technologies Inc., San Diego, CA, USA; Catalogue No. AT104) using standard tissue culture methods and resuspended in media to give 5.5x10⁴ cells per ml. Aliquots (90 µl) were seeded into each of the inner 60 wells of a black ‘Costar’ 96-well plate (Corning Inc., NY, USA; Catalogue No. 3904) to give a density of ~5000 cells per well. Aliquots (90 µl) of culture media were placed in the outer wells to prevent edge effects. [An alternative cell handling procedure involved the maintenance of the cells in a ‘SelecT’ robotic device (The Automation Partnership, Royston, Herts SG8 5WY, UK). Cells were resuspended in media to give 5 x10⁴ cells per ml. Aliquots (100 µl) were seeded into the wells of a black 30 ‘Costar’ 96-well plate.] The cells were incubated overnight at 37°C with 5% CO₂ to allow them to adhere.

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On day 2, the cells were treated with test compounds. Test compounds were prepared as 10 mM stock solutions in DMSO and serially diluted as required with DMSO and with growth media to give a range of concentrations that were 10-fold the required final test concentrations. Aliquots (10 µl) of each compound dilution were placed in duplicate wells to give the final required concentrations. As a minimum response control, each plate contained wells having a final concentration of 30 µM LY294002 (Calbiochem, Beeston, UK, Catalogue No. 440202). As a maximum response control, wells contained 0.5% DMSO instead of test compound. [An alternative cell treatment procedure involved the transfer of test compounds to the wells using an 'Echo 550' liquid dispenser (Labcyte Inc., Sunnyvale, CA 94089, USA). Test compounds were prepared as 10mM stock solutions in DMSO and aliquots (40 µl) of each compound were dispensed into one well of a quadrant of wells within a 384-well plate (Labcyte Inc., Catalogue No. P-05525-CV1). Four concentrations of each compound were prepared in each quadrant of wells in the 384-well plate using a 'Hydra II' pipettor (Matrix Technologies Corporation, Handforth SK9 3LP, UK). Using a 'Quadra Tower' liquid pipetting system (Tomtec Inc., Hamden, CT 06514, USA) and the 'Echo 550' liquid dispenser, the required concentration of each compound was placed in specific wells in duplicate.] The treated cells were incubated for 2 hours at 37°C with 5% CO₂.

Following incubation, the contents of the plates were fixed by treatment with a 1.6% aqueous formaldehyde solution (Sigma, Poole, Dorset, UK, Catalogue No. F1635) at room temperature for 30 minutes.

All subsequent aspiration and washing steps were carried out using a Tecan 96-well plate washer (aspiration speed 10 mm/sec). The fixing solution was removed and the contents of the plates were washed with phosphate-buffered saline (PBS; 50 µl; such as that available from Gibco, Catalogue No. 10010015). The contents of the plates were treated at room temperature for 1 hour with an aliquot (50 µl) of a cell permeabilisation/blocking buffer consisting of a mixture of PBS, 0.5% Tween-20 and 5% dried skimmed milk ['Marvel' (registered trade mark); Premier Beverages, Stafford, GB]. The permeabilisation/blocking buffer caused the cell wall to be partially degraded to allow immunostaining to proceed whilst blocking non-specific binding sites. The buffer was removed and the cells were incubated for 16 hours at 4°C with rabbit anti-phospho-Akt (Ser473) antibody solution (50 µl per well; Cell Signaling Technology Inc., Hitchin, Herts, U.K., Catalogue No. 3787) that had been diluted 1:500 in 'blocking' buffer consisting of a mixture of PBS, 0.5% Tween-20 and 5%

dried skimmed milk. Cells were washed three times in a mixture of PBS and 0.05% Tween-20. Subsequently, cells were incubated for 1 hour at 4°C with Alexafluor488 labelled goat anti-rabbit IgG (50 µl per well; Molecular Probes, Invitrogen Limited, Paisley, UK, Catalogue No. A11008) that had been diluted 1:500 in ‘blocking’ buffer. Cells were washed 3 times with 5 a mixture of PBS and 0.05% Tween-20. An aliquot of PBS containing 1.6% aqueous formaldehyde (50 µl) was added to each well. After 15 minutes, the formaldehyde was removed and each of the wells was washed with PBS (100 µl). An aliquot of PBS (50 µl) was added to each well and the plates were sealed with black plate sealers and the fluorescence signal was detected and analysed.

10 Fluorescence dose response data obtained with each compound were analysed and the degree of inhibition of Serine 473 in Akt was expressed as an IC₅₀ value.

(d) In Vitro MDA-MB-468 human breast adenocarcinoma Proliferation Assay

15 This assay determines the ability of test compounds to inhibit cell proliferation, as assessed by the extent of metabolism by living cells of a tetrazolium dye. A MDA-MB-468 human breast carcinoma cell line (ATCC, Catalogue No. HTB-132) was routinely maintained as described in Biological Assay (c) hereinbefore except that the growth medium did not contain phenol red.

20 For the proliferation assay, the cells were detached from the culture flask using ‘Accutase’ and, at a density of 4000 cells per well in 100 µl of complete growth medium, the cells were placed in wells in a ‘Costar’ 96-well tissue culture-treated plate (Corning Inc., Catalogue No. 3598). Aliquots (100 µl) per well of growth medium were added to some wells to provide blank values for the colorometric measurement. The cells were incubated overnight at 37°C with 5% CO₂ to allow them to adhere.

25 Sufficient phenazine ethosulphate (PES, Sigma Catalogue No. P4544) was added to a 1.9 mg/ml solution of 3-(4, 5-dimethylthiazol-2-yl)-5-(3 carboxymethoxyphenyl)-2-(4-sulphophenyl)-2H-tetrazolium salt (MTS; Promega UK, Southampton SO16 7NS, UK; Catalogue No. G1111) to give a 0.3 mM PES solution. An aliquot (20 µl) of the resultant MTS/PES solution was added to each well of one plate. The cells were incubated for 2 hours at 37°C with 5% CO₂ and the optical density was measured on a plate reader using a wavelength of 492nm. The relative cell number at the commencement of the assay was thereby measured.

Test compounds were prepared as 10 mM stock solutions in DMSO and serially diluted with growth medium to give a range of test concentrations. An aliquot (50 µl) of each compound dilution was placed in a well in the 96-well plates. Each plate contained control wells without test compound. With the exception of wells containing the plate blanks, the outer wells on each 96-well plate were not used. The cells were incubated for 72 hours at 37°C with 5% CO₂. An aliquot (30 µl) of the MTS/PES solution was added to each well and the cells were incubated for 2 hours at 37°C with 5% CO₂. The optical density was measured on a plate reader using a wavelength of 492nm.

Dose response data were obtained for each test compound and the degree of inhibition of MDA-MB-468 cell growth was expressed as an IC₅₀ value.

(e) In Vivo MDA-MB-468 Xenograft Growth Assay

This test measures the ability of compounds to inhibit the growth of MDA-MB-468 human breast adenocarcinoma cells grown as a tumour in athymic nude mice (Alderley Park nu/nu strain). A total of about 5 x 10⁶ MDA-MB-468 cells in matrigel (Beckton Dickinson Catalogue No. 40234) are injected subcutaneously into the left flank of each test mouse and the resultant tumours are allowed to grow for about 14 days. Tumour size is measured twice weekly using callipers and a theoretical volume is calculated. Animals are selected to provide control and treatment groups of approximately equal average tumour volume. Test compounds are prepared as a ball-milled suspension in 1% polysorbate vehicle and dosed orally once daily for a period of about 28 days. The effect on tumour growth is assessed.

Although the pharmacological properties of the compounds of the Formula I will vary with structural change as expected, in general activity possessed by compounds of the Formula I, may be demonstrated at the following concentrations or doses in one or more of the above tests (a), (b), (c), (d) and (e) :-

- Test (a):- IC₅₀ versus p110α Type Ia human PI3K in the range, for example, 0.01 - 5 µM;
- Test (b):- IC₅₀ versus mTOR PI kinase-related kinase in the range, for example, 0.1 - 10 µM;
- Test (c):- IC₅₀ in the range, for example, 0.01 - 5 µM;
- Test (d):- IC₅₀ in the range, for example, 0.05 - 20 µM;
- Test (e):- activity in the range, for example, 1-200 mg/kg/day.

For example, the pyrimidine compound disclosed within Example 1 possesses activity in Test (a) with an IC₅₀ versus p110 α Type Ia human PI3K of approximately 0.2 μ M, and in Test (c) with an IC₅₀ of approximately 0.01 μ M. For example, the pyrimidine compound disclosed within Example 2 possesses activity in Test (a) with an IC₅₀ versus p110 α Type Ia human PI3K of approximately 0.6 μ M, and in Test (c) with an IC₅₀ of approximately 0.2 μ M.

No untoward toxicological effects are expected when a compound of Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore is administered at the dosage ranges defined hereinafter.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

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

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

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 1 mg to 1 g of active agent (more suitably from 1 to 250 mg, for example from 1 to 100 mg) compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of the

Formula I will naturally vary according to the nature and severity of the disease state, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 1 mg/kg to 100 mg/kg body weight is received, given if required in divided doses. In general, lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 1 mg/kg to 25 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 1 mg/kg to 25 mg/kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 10 mg to 0.5 g of a compound of this invention.

As stated above, it is known that PI3K enzymes contribute to tumourigenesis by one or more of the effects of mediating proliferation of cancer and other cells, mediating angiogenic events and mediating the motility, migration and invasiveness of cancer cells. We have found that the pyrimidine derivatives of the present invention possess potent anti-tumour activity which it is believed is obtained by way of inhibition of one or more of the Class I PI3K enzymes (such as the Class Ia PI3K enzymes and/or the Class Ib PI3K enzyme) and/or a mTOR kinase (such as a mTOR PI kinase-related kinase) that are involved in the signal transduction steps which lead to the proliferation and survival of tumour cells and the invasiveness and migratory ability of metastasising tumour cells.

Accordingly, the derivatives of the present invention are of value as anti-tumour agents, in particular as selective inhibitors of the proliferation, survival, motility, dissemination and invasiveness of mammalian cancer cells leading to inhibition of tumour growth and survival and to inhibition of metastatic tumour growth. Particularly, the pyrimidine derivatives of the present invention are of value as anti-proliferative and anti-invasive agents in the containment and/or treatment of solid tumour disease. Particularly, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours which are sensitive to inhibition of one or more of the multiple PI3K enzymes such as the Class Ia PI3K enzymes and the Class Ib PI3K enzyme that are involved in the signal transduction steps which lead to the proliferation and survival of tumour cells and the migratory ability and invasiveness of metastasising tumour cells. Further, the compounds of the present invention are expected to

be useful in the prevention or treatment of those tumours which are mediated alone or in part by inhibition of PI3K enzymes such as the Class Ia PI3K enzymes and the Class Ib PI3K enzyme, *i.e.* the compounds may be used to produce a PI3K enzyme inhibitory effect in a warm-blooded animal in need of such treatment.

5 As stated hereinbefore, inhibitors of PI3K enzymes should be of therapeutic value for treatment of, for example, cancer of the breast, colorectum, lung (including small cell lung cancer, non-small cell lung cancer and bronchioalveolar cancer) and prostate, and of cancer of the bile duct, bone, bladder, head and neck, kidney, liver, gastrointestinal tissue, oesophagus, ovary, pancreas, skin, testes, thyroid, uterus, cervix and vulva, and of leukaemias [including 10 acute lymphocytic leukaemia (ALL) and chronic myelogenous leukaemia (CML)], multiple myeloma and lymphomas.

According to a further aspect of the invention there is provided a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use as a medicament in a warm-blooded animal such as man.

15 According to a further aspect of the invention, there is provided a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a 20 pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use in a warm-blooded animal such as man as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

According to a further aspect of the invention, there is provided the use of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for the production of an anti-proliferative effect in a warm-blooded animal such 25 as man.

According to a further feature of this aspect of the invention there is provided the use of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore as an anti-invasive agent in the containment and/or treatment of solid tumour disease in a warm-blooded animal such as man.

30 According to a further feature of this aspect of the invention there is provided the use of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as

defined hereinbefore in the manufacture of a medicament for use in the production of an anti-proliferative effect in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided the use of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in a warm-blooded animal such as man as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-proliferative effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a pyrimidine derivative of the Formula I, 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 anti-invasive effect by the containment and/or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further aspect of the invention there is provided the use of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of solid tumour disease 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 the prevention or treatment of solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further feature of this aspect of the invention there is provided a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

According to a further aspect of the invention there is provided the use of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined

hereinbefore for the prevention or treatment of solid tumour disease in a warm-blooded animal such as man.

According to a further aspect of the invention there is provided a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use in the prevention or treatment of those tumours which are sensitive to inhibition of PI3K enzymes (such as the Class Ia enzymes and/or the Class Ib PI3K enzyme) and/or a mTOR kinase (such as a mTOR PI kinase-related kinase) that are involved in the signal transduction steps which lead to the proliferation, survival, invasiveness and migratory ability of tumour cells.

According to a further feature of this aspect of the invention there is provided the use of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the prevention or treatment of those tumours which are sensitive to inhibition of PI3K enzymes (such as the Class Ia enzymes and/or the Class Ib PI3K enzyme) and/or a mTOR kinase (such as a mTOR PI kinase-related kinase) that are involved in the signal transduction steps which lead to the proliferation, survival, invasiveness and migratory ability of tumour cells.

According to a further feature of this aspect of the invention there is provided a method for the prevention or treatment of those tumours which are sensitive to inhibition of PI3K enzymes (such as the Class Ia enzymes and/or the Class Ib PI3K enzyme) and/or a mTOR kinase (such as a mTOR PI kinase-related kinase) that are involved in the signal transduction steps which lead to the proliferation, survival, invasiveness and migratory ability of tumour cells which comprises administering to said animal an effective amount of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further feature of this aspect of the invention there is provided the use of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for the prevention or treatment of those tumours which are sensitive to inhibition of PI3K enzymes (such as the Class Ia enzymes and/or the Class Ib PI3K enzyme) and/or a mTOR kinase (such as a mTOR PI kinase-related kinase) that are involved in the signal transduction steps which lead to the proliferation, survival, invasiveness and migratory ability of tumour cells.

According to a further aspect of the invention there is provided a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use in providing a PI3K enzyme inhibitory effect (such as a Class Ia PI3K enzyme or Class Ib PI3K enzyme inhibitory effect) and/or a mTOR kinase inhibitory effect (such as a mTOR PI kinase-related kinase inhibitory effect).
5

According to a further feature of this aspect of the invention there is provided the use of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in providing a PI3K enzyme inhibitory effect (such as a Class Ia PI3K enzyme or Class Ib PI3K enzyme inhibitory effect) and/or a mTOR kinase inhibitory effect (such as a mTOR PI kinase-related kinase inhibitory effect).
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According to a further feature of this aspect of the invention there is also provided a method for providing a PI3K enzyme inhibitory effect (such as a Class Ia PI3K enzyme or Class Ib PI3K enzyme inhibitory effect) and/or a mTOR kinase inhibitory effect (such as a mTOR PI kinase-related kinase inhibitory effect) which comprises administering an effective amount of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.
15

According to a further feature of this aspect of the invention there is provided the use of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for providing a PI3K enzyme inhibitory effect (such as a Class Ia PI3K enzyme or Class Ib PI3K enzyme inhibitory effect) and/or a mTOR kinase inhibitory effect (such as a mTOR PI kinase-related kinase inhibitory effect).
20

As stated hereinbefore, certain compounds of the present invention, possess substantially better potency against Class Ia PI3K enzymes or against the Class Ib PI3K enzyme than against EGF receptor tyrosine kinase, VEGF receptor tyrosine kinase or Src non-receptor tyrosine kinase enzymes. Such compounds possess sufficient potency against Class Ia PI3K enzymes or the Class Ib PI3K enzyme that they may be used in an amount sufficient to inhibit PI3K enzymes whilst demonstrating little activity against EGF receptor tyrosine kinase, VEGF receptor tyrosine kinase or Src non-receptor tyrosine kinase enzymes. Such compounds are likely to be useful for the selective inhibition of PI3K enzymes and are likely to be useful for the effective treatment of, for example Class Ia PI3K enzyme driven tumours.
25
30

According to this aspect of the invention there is provided a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use in providing a selective PI3K enzyme inhibitory effect.

According to a further feature of this aspect of the invention there is provided the use of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in providing a selective PI3K enzyme inhibitory effect.

According to a further feature of this aspect of the invention there is also provided a method for providing a selective PI3K enzyme inhibitory effect which comprises 10 administering an effective amount of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further feature of this aspect of the invention there is provided the use of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for providing a selective PI3K enzyme inhibitory effect.

By "a selective PI3K enzyme inhibitory effect" is meant that the pyrimidine derivatives of the Formula I are more potent against PI3K enzymes than against other kinase enzymes. In particular, some of the compounds according to the invention are more potent against PI3K enzymes than against other kinases such as receptor or non-receptor tyrosine kinases or serine/threonine kinases. For example a selective PI3K enzyme inhibitor according to the 20 invention is at least 5 times more potent, preferably at least 10 times more potent, more preferably at least 100 times more potent, against PI3K enzymes than against other kinases.

According to a further feature of the invention there is provided a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use in the treatment of cancer of the breast, colorectum, lung (including small cell lung cancer, 25 non-small cell lung cancer and bronchioalveolar cancer) and prostate.

According to a further feature of this aspect of the invention there is provided a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use in the treatment of cancer of the bile duct, bone, bladder, head and neck, kidney, liver, gastrointestinal tissue, oesophagus, ovary, pancreas, skin, testes, thyroid, 30 uterus, cervix and vulva, and of leukaemias (including ALL and CML), multiple myeloma and lymphomas.

According to a further feature of this aspect of the invention there is provided the use of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of cancer of the breast, colorectum, lung (including small cell lung cancer, non-small cell lung cancer and bronchioalveolar cancer) and prostate.

According to a further feature of this aspect of the invention there is provided the use of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of cancer of the bile duct, bone, bladder, head and neck, kidney, liver, gastrointestinal tissue, oesophagus, ovary, pancreas, skin, testes, thyroid, uterus, cervix and vulva, and of leukaemias (including ALL and CML), multiple myeloma and lymphomas.

According to a further feature of this aspect of the invention there is provided a method for treating cancer of the breast, colorectum, lung (including small cell lung cancer, non-small cell lung cancer and bronchioalveolar cancer) and prostate in a warm blooded animal such as man that is in need of such treatment which comprises administering an effective amount of a pyrimidine derivative of the Formula I, 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 treating cancer of the bile duct, bone, bladder, head and neck, kidney, liver, gastrointestinal tissue, oesophagus, ovary, pancreas, skin, testes, thyroid, uterus, cervix and vulva, and of leukaemias (including ALL and CML), multiple myeloma and lymphomas in a warm blooded animal such as man that is in need of such treatment which comprises administering an effective amount of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore.

According to a further feature of this aspect of the invention there is provided the use of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for treating cancer of the breast, colorectum, lung (including small cell lung cancer, non-small cell lung cancer and bronchioalveolar cancer) and prostate.

According to a further feature of this aspect of the invention there is provided the use of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for treating cancer of the bile duct, bone, bladder, head and neck, kidney,

liver, gastrointestinal tissue, oesophagus, ovary, pancreas, skin, testes, thyroid, uterus, cervix and vulva, and of leukaemias (including ALL and CML), multiple myeloma and lymphomas.

As stated hereinbefore, 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.

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

- (i) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea and gemcitabine); 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, taxoids like taxol and taxotere, and poloquinase 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 5 α -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 bosutinib (SKI-606), and metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function];

- (iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies [for example the anti-erbB2 antibody trastuzumab and the anti-erbB1 antibodies cetuximab (C225) and panitumumab]; such inhibitors also include, for example, tyrosine kinase inhibitors [for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as gefitinib (ZD1839), erlotinib (OSI-774) and CI 1033, and erbB2 tyrosine kinase inhibitors such as lapatinib), inhibitors of the hepatocyte growth factor family, inhibitors of the insulin growth factor receptor, inhibitors of the platelet-derived growth factor family and/or bcr/abl kinase such as imatinib, dasatinib (BMS-354825) and nilotinib (AMN107), inhibitors of cell signalling through MEK, AKT, PI3, c-kit, and/or aurora kinases]; such inhibitors also include cyclin dependent kinase inhibitors including CDK2 and CDK4 inhibitors; and such inhibitors also include, for example, inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006), tipifarnib (R115777) and lonafarnib (SCH66336));
- (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 (AvastinTM) and VEGF receptor tyrosine kinase inhibitors such as vandetanib (ZD6474), vatalanib (PTK787), sunitinib (SU11248) and 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function and angiostatin)];
- (vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;
- (vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;
- (viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as 5 cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and 10 the other pharmaceutically-active agent within its approved dosage range.

According to this aspect of the invention there is provided a pharmaceutical product comprising a pyrimidine derivative of the formula I as defined hereinbefore and an additional anti-tumour agent as defined hereinbefore for the conjoint treatment of cancer.

Although the compounds of the Formula I are primarily of value as therapeutic agents 15 for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of PI3K enzymes. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

The invention may be illustrated by representative Examples in which, generally :

20 (i) operations may be 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;

25 (ii) reactions conducted under microwave radiation may be performed using an instrument such as a ‘Smith Synthesiser’ (300 KWatts) on either the normal or high setting, which instrument makes use of a temperature probe to adjust the microwave power output automatically in order to maintain the required temperature; alternatively an ‘Emrys Optimizer’ microwave instrument may be used;

(iii) in general, the course of reactions may be 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;

30 (iv) when necessary, organic solutions may be dried over anhydrous magnesium sulphate, work-up procedures were carried out after removal of residual solids by filtration, evaporation were carried out by rotary evaporation *in vacuo*;

(v) 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;

(vi) in general, the structures of the end-products of the Formula I may be 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 or a Bruker Avance spectrometer operating at a field strength of 400 MHz; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad;

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

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

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

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

(xi) analytical HPLC methods selected from those listed below may be used; in general, reversed-phase silica was used with a flow rate of about 1ml per minute and detection was by Electrospray Mass Spectrometry and by UV absorbance using a diode array detector over a wavelength of 220 to 300 nm; for each method Solvent A:was water and Solvent B was acetonitrile:-

Method A1 : Phenomenex Syngi MAX-RP 80Å column (4 microns silica, 2.1 mm diameter, 50 mm length) using a Solvent C comprising 0.1% aqueous ammonium hydroxide ($d=0.88$) in deionised water and a solvent gradient over 4 minutes from a 90:5:5 mixture of Solvents A, B and C respectively to a 95:5 mixture of Solvents B and C;

Method A2 : Phenomenex 'Gemini' RP 110Å column (5 microns silica, 2 mm diameter, 50 mm length) using a Solvent C comprising 0.1% aqueous ammonium hydroxide (d=0.88)) and a solvent gradient over 4 minutes from a 5:95 mixture of Solvents B and C to a 95:5 mixture of Solvents B and C;

5 Method B1 : Phenomenex Synergi MAX-RP 80Å column (4 microns silica, 2.1 mm diameter, 50 mm length) using a Solvent C comprising a 1:1 mixture of water and acetonitrile (the mixture containing 1% formic acid) and a solvent gradient over 4 minutes from a 90:5:5 mixture of Solvents A, B and C respectively to a 95:5 mixture of Solvents B and C;

10 Method B2 : Phenomenex Synergi MAX-RP 80Å column (4 microns silica, 2.1 mm diameter, 50 mm length) using a Solvent C comprising a 1:1 mixture of water and acetonitrile (the mixture containing 1% formic acid) and a solvent gradient over 4 minutes from a 95:5 mixture of Solvents A and C to a 58:37:5 mixture of Solvents A, B and C respectively;

15 (xii) 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;

20 (xiii) one or more of the following abbreviations may be used : -

DMSO dimethylsulphoxide

THF tetrahydrofuran

25 DMF *N,N*-dimethylformamide

DMA *N,N*-dimethylacetamide

Example 1

2-[1-[4-[2-(Difluoromethyl)benzoimidazol-1-yl]-6-morpholin-4-yl-pyrimidin-2-yl]-4-piperidyl]ethanamine

25 A mixture of 1-(2-chloro-6-morpholin-4-yl-pyrimidin-4-yl)-2-(difluoromethyl)benzoimidazole (0.100 g), *tert*-butyl N-[2-(4-piperidyl)ethyl]carbamate (0.093 g) and sodium carbonate (0.086 g) in DMF (3 ml) was heated in a sealed vessel in a microwave at 100°C for 40 minutes. The resultant reaction mixture was allowed to cool to ambient temperature and was then diluted with water and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried over magnesium sulfate and evaporated. The residue was taken into dichloromethane (2 ml) and trifluoroacetic acid (2 ml), stirred at

ambient temperature for 1 hour and evaporated. The residue was purified by HPLC using a Waters 'Xterra' preparative reversed-phase column (5 microns silica, 19 mm diameter, 100 mm length) using decreasingly polar mixtures of water [containing 1% aqueous ammonium hydroxide ($d=0.88$)] and acetonitrile as eluent. There was thus obtained the title compound
5 (0.082 g); NMR Spectrum: (DMSO_d₆ at 373K) 1.12 - 1.21 (m, 2H), 1.35 - 1.40 (m, 2H), 1.67 - 1.72 (m, 1H), 1.72 - 1.77 (m, 2H), 2.65 (t, 2H), 2.92 - 2.98 (m, 4H), 3.65 - 3.68 (m, 4H), 3.72 - 3.75 (m, 4H), 4.53 - 4.58 (m, 2H), 6.26 (s, 1H), 7.32 - 7.54 (t, 1H), 7.39 - 7.47 (m, 2H), 7.74 (d, 1H), 7.84 (d, 1H); Mass Spectrum: M+H⁺ 458.

10 The 1-(2-chloro-6-morpholin-4-yl-pyrimidin-4-yl)-2-(difluoromethyl)benzoimidazole used as a starting material was prepared as follows:-

A mixture of 1,2-phenylenediamine (54.1 g) and ethyl difluoroacetate (57.8 ml) in toluene (350 ml) was heated under nitrogen to 87°C for 41 hours, filtered whilst hot and evaporated. The residue was dissolved in a mixture of THF (200 ml) and dichloromethane (200 ml), filtered through silica (30 g) and evaporated to a solid, which solid was washed with a 2:1 mixture of isohexane and dichloromethane. There was thus obtained 2-difluoromethyl-
15 1H-benzimidazole (64.8 g); NMR Spectrum: (DMSO_d₆) 7.28 (t, 1H), 7.29-7.34 (m, 2H), 7.66-7.68 (m, 2H), 13.30 (s, 1H). Mass Spectrum: M+H⁺ 169. A mixture of the material so obtained (7.57 g), 4-(2,6-dichloropyrimidin-4-yl)morpholine (11.7 g), sodium bicarbonate (21.0 g) and DMF (100 ml) was stirred under nitrogen at 110°C for 20 hours, cooled to
20 ambient temperature, filtered and evaporated. The residue was chromatographed on silica eluting with increasing proportions of ethyl acetate in dichloromethane. The solid obtained, which was a mixture of the major and minor isomeric products, was washed with a mixture of diethyl ether (400 ml) and iso-hexane (400 ml) and the washings were evaporated to a residue,
25 [A]. The washed solid was recrystallised from dichloromethane (30 ml) by addition of iso-hexane (120 ml) and the crystalline solid was filtered off, washed with a mixture of diethyl ether (300 ml) and iso-hexane (300 ml) and the washings were again evaporated to a residue,
[B]. Residues [A] and [B] were combined and purified using a Waters 'Xterra' preparative reversed-phase column (5 microns silica, 19 mm diameter, 100 mm length) using decreasingly polar mixtures of water [containing 1% aqueous ammonium hydroxide ($d = 0.88$)] and
30 acetonitrile as eluent. There was thus obtained 1-(2-chloro-6-morpholin-4-yl-pyrimidin-4-yl)-2-(difluoromethyl)benzoimidazole (0.173 g); NMR Spectrum: (DMSO_d₆) 3.73 (s, 8H), 7.20 (s,

1H), 7.44-7.52 (m, 2H), 7.51 (t, 1H), 7.77-7.79 (m, 1H), 7.88-7.90 (m, 1H). Mass Spectrum: M+H⁺ 366.

Example 2

5 **(2S)-N-[1-[4-[2-(difluoromethyl)benzoimidazol-1-yl]-6-morpholin-4-yl-pyrimidin-2-yl]-4-piperidyl]piperidine-2-carboxamide**

A mixture of (2S)-1-[(2-methylpropan-2-yl)oxygen carbonyl]piperidine-2-carboxylic acid (0.069 g), 2-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.114 g), triethylamine (0.126 ml) and DMF (0.5 ml) was stirred at ambient temperature for 15 minutes to give Solution A. Solution A was added to a mixture of 1-[4-[2-(difluoromethyl)benzoimidazol-1-yl]-6-morpholin-4-yl-pyrimidin-2-yl]piperidin-4-amine (0.089 g) and DMF (0.5ml). The resultant reaction mixture was stirred at ambient temperature under nitrogen for 30 minutes. A second Solution A was prepared and added to the reaction mixture. The resultant reaction mixture was stirred at ambient temperature for a further 15 minutes and then the reaction mixture was evaporated in a centrifugal evaporator. The residue was taken into dichloromethane (1 ml) and trifluoroacetic acid (1 ml), stirred at ambient temperature for 1 hour, treated with more trifluoroacetic acid (1 ml), and evaporated. The residue was dissolved in methanol (5 ml) and added to an Isolute SCX-3 cation exchange cartridge (5 g, International Sorbent Technology Limited, Mid Glamorgan, UK), followed by methanol (30 ml). The product was then eluted by addition of a 7M solution of ammonia in methanol (15 ml) and after evaporation was further purified by HPLC using a Waters "Xbridge" preparative reversed-phase column (5 microns silica, 19 mm diameter, 100 mm length) using decreasingly polar mixtures of water [containing 1% aqueous ammonium hydroxide (d=0.88)] and acetonitrile as eluent. There was thus obtained the title compound (0.020 g); NMR Spectrum: (DMSO_d₆) 1.26-1.46 (m, 6H), 1.72-1.78 (m, 4H), 2.48-2.55 (m, 2H), 2.88 (m, 1H), 3.00-3.08 (m, 3H), 3.68-3.70 (d, 8H), 3.82-3.89 (m, 1H), 4.50 (d, 2H), 6.38 (s, 1H), 7.39-7.49 (m, 3H), 7.51-7.52 (t, 1H), 7.76 (d, 1H), 7.87 (d, 1H). Mass Spectrum: M+H⁺ 598.

The 1-[4-[2-(difluoromethyl)benzoimidazol-1-yl]-6-morpholin-4-yl-pyrimidin-2-yl]piperidin-4-amine used as a starting material was prepared as follows:-

A mixture of *tert*-butyl N-[1-[4-chloro-6-[[2-[(2,2-difluoroacetyl)amino]phenyl]amino]pyrimidin-2-yl]-4-piperidyl]carbamate (612 mg),

morpholine (538 ul) and DMA (6 ml) was heated in a sealed vessel in a microwave at 200°C for 30 minutes, cooled to ambient temperature and then evaporated. There was thus obtained a partly deprotected mixture of *tert*-butyl N-[1-[4-[2-(difluoromethyl)benzoimidazol-1-yl]-6-morpholin-4-yl-pyrimidin-2-yl]-4-piperidyl]carbamate and 1-[4-[2-(difluoromethyl)benzoimidazol-1-yl]-6-morpholin-4-yl-pyrimidin-2-yl]piperidin-4-amine, which was used without further purification. This was taken into dichloromethane (0.5 ml) and trifluoroacetic acid (0.5 ml), stirred for 30 minutes at ambient temperature under nitrogen, treated with more trifluoroacetic acid (1 ml), and stirred at ambient temperature for a further hour. The resultant mixture was stirred while 2M aqueous sodium carbonate solution (5 ml) was added dropwise, then the organic layer was separated and the aqueous layer washed three times with dichloromethane (5 ml). The dichloromethane solutions were combined, dried over magnesium sulfate, and evaporated. The product was purified by chromatography on silica eluting with increasing amounts in dichloromethane of a 10% solution of aqueous ammonia ($d=0.88$) in methanol. There was thus obtained 1-[4-[2-(difluoromethyl)benzoimidazol-1-yl]-6-morpholin-4-yl-pyrimidin-2-yl]piperidin-4-amine (0.335 g); NMR Spectrum: (DMSO_d₆) 1.26 (d, 2H), 1.80-1.84 (m, 2H), 2.97-3.00 (m, 3H), 3.68-3.71 (m, 8H), 4.51 (d, 2H), 6.37 (s, 1H), 7.42-7.47 (m, 2H), 7.52 (t, 1H), 7.75-7.77 (m, 1H), 7.85-7.88 (m, 1H). Mass Spectrum: M+H⁺ 430.

The *tert*-butyl N-[1-[4-chloro-6-[[2-[2,2-difluoroacetyl]amino]phenyl]amino]pyrimidin-2-yl]-4-piperidyl]carbamate used as a starting material was prepared as follows:-

A mixture of N-[2-[(2,6-dichloropyrimidin-4-yl)amino]phenyl]-2,2-difluoro-acetamide (0.833 g), *tert*-butyl N-(4-piperidyl)carbamate (0.501 g), sodium hydrogen carbonate (0.841 g) and DMF (2 ml) was heated to 70°C and stirred at this temperature for 30 minutes. The resultant reaction mixture was then cooled to ambient temperature, filtered and evaporated. The product was purified by chromatography on silica eluting with increasing proportions of ethyl acetate in dichloromethane. There was thus obtained *tert*-butyl N-[1-[4-chloro-6-[[2-[2,2-difluoroacetyl]amino]phenyl]amino]pyrimidin-2-yl]-4-piperidyl]carbamate (0.880 g); NMR Spectrum: (DMSO_d₆) 1.24-1.29 (m, 2H), 1.39 (s, 9H), 1.73-1.79 (m, 2H), 2.93 (t, 2H), 3.50 (d, 1H), 4.35-4.38 (m, 2H), 5.96 (s, 1H), 6.39 (t, 1H), 6.86 (d, 1H), 7.18-7.23 (m, 1H), 7.25-7.30 (m, 1H), 7.56-7.59 (m, 1H), 7.62-7.64 (m, 1H), 8.90 (s, 1H), 10.16 (s, 1H). Mass Spectrum: M-H⁺ 495.

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The N-[2-[(2,6-dichloropyrimidin-4-yl)amino]phenyl]-2,2-difluoro-acetamide used as a starting material was prepared as follows:-

A mixture of 2,2-difluoro-N-(2-nitrophenyl)acetamide (7.57 g), N,N,N',N'-tetramethylnaphthalene-1,8-diamine (8.25 g) and ethyl acetate (350 ml) was hydrogenated 5 using an Asynt Technologies H-Cube at a pressure of 1 bar with full hydrogen setting and a flow-rate of 1ml/minute to give after evaporation a residue which was taken into DMA (80 ml). The solution was treated with 2,4,6-trichloropyrimidine (7.06 g) and stirred at ambient temperature under nitrogen for 64 hours. The mixture was evaporated at 30°C and the residue was taken into ethyl acetate (100 ml), filtered and the filtrate evaporated. The resultant residue 10 was purified by chromatography on silica eluting with a gradient from isohexane:dichloromethane:ethyl acetate 50:50:2 to dichloromethane:ethyl acetate 5:1. This gave N-[2-[(2,6-dichloropyrimidin-4-yl)amino]phenyl]-2,2-difluoro-acetamide (10.25 g); NMR Spectrum: (DMSO_d₆) 6.36 (t, 1H), 6.59 (s, 1H), 7.31-7.36 (m, 2H), 7.50-7.54 (m, 1H), 7.60-7.65 (m, 1H) Mass Spectrum: M+H⁺ 331.

15 The 2,2-difluoro-N-(2-nitrophenyl)acetamide used as a starting material was prepared as follows:-

A mixture of 2-nitroaniline (10.36 g) and zirconium IV chloride (0.175 g) was heated under nitrogen to 90°C. The heat source was removed and difluoroacetic anhydride (8.27 ml) was added dropwise over 10 minutes, the temperature being maintained at 97 to 103°C. The 20 resultant mixture was allowed to cool to 30°C and diluted with ether (250 ml). The solution was filtered through silica (5 g), then evaporated to 50 ml. Isohexane (100 ml) was added slowly and the mixture stood at 0°C overnight and was then filtered to give 2,2-difluoro-N-(2-nitrophenyl)acetamide (13.37 g); NMR Spectrum: (DMSO_d₆) 6.50 (t, 1H), 7.49-7.53 (m, 1H), 7.74 (d, 1H), 7.78-7.82 (m, 1H), 8.05-8.07 (m, 1H), 11.09 (s, 1H) Mass Spectrum: M+H⁺ 215.

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Example 3

(2R)-N-[1-[4-[2-(difluoromethyl)benzimidazol-1-yl]-6-morpholin-4-yl-pyrimidin-2-yl]-4-piperidyl]-2-methylamino-3-phenyl-propanamide

Using an analogous procedure to that described in Example 2, (2R)-2-[methyl-[(2-methylpropan-2-yl)oxycarbonyl]amino]-3-phenyl-propanoic acid (0.084 g) was reacted with 30 1-[4-[2-(difluoromethyl)benzimidazol-1-yl]-6-morpholin-4-yl-pyrimidin-2-yl]piperidin-4-amine (0.083 g) to give the title compound (0.087 g); NMR Spectrum: (DMSO_d₆) 1.20-1.34

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(m, 3H), 1.64 (d, 1H), 1.74 (d, 2H), 2.17 (s, 3H), 2.71-2.80 (m, 2H), 3.06-3.10 (m, 2H), 3.66 (s, 4H), 3.70 (d, 4H), 3.85 (m, 1H), 4.37-4.45 (m, 2H), 6.37 (s, 1H), 7.18 (t, 3H), 7.25 (m, 2H), 7.42-7.47 (m, 2H), 7.50 (t, 1H), 7.67 (m, 1H), 7.76 (d, 1H), 7.87 (d, 1H). Mass Spectrum: M+H⁺ 591.

5

Example 4

2-amino-N-[1-[4-[2-(difluoromethyl)benzoimidazol-1-yl]-6-morpholin-4-yl-pyrimidin-2-yl]-4-piperidyl]acetamide

Using an analogous procedure to that described in Example 2, 2-[(2-methylpropan-2-yl)oxycarbonylamino]acetic acid (0.053 g) was reacted with 1-[4-[2-(difluoromethyl)benzoimidazol-1-yl]-6-morpholin-4-yl-pyrimidin-2-yl]piperidin-4-amine (0.083 g) to give the title compound (0.038 g); NMR Spectrum: (DMSO_d₆) 1.39 (m, 2H), 1.79-1.81 (m, 2H), 3.04-3.10 (m, 4H), 3.69 (d, 5H), 3.70 (d, 3H), 3.88 (m, 1H), 4.50 (d, 2H), 6.38 (s, 1H), 7.40-7.45 (m, 2H), 7.52 (t, 1H), 7.71 (d, 1H), 7.76 (d, 1H), 7.87 (d, 1H). Mass Spectrum: M+H⁺ 487.

Example 5

(2S)-N-[1-[4-[2-(difluoromethyl)-2,3-dihydrobenzoimidazol-1-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]-4-piperidyl]pyrrolidine-2-carboxamide

A mixture of (2S)-1-[(2-methylpropan-2-yl)oxycarbonyl]pyrrolidine-2-carboxylic acid (0.065 g), 2-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.114 g), triethylamine (0.126 ml) and DMF (0.5 ml) was stirred at ambient temperature for 15 minutes to give Solution A. Solution A was added to a mixture of 1-[4-[2-(difluoromethyl)benzoimidazol-1-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]piperidin-4-amine (79% pure, 0.049 g) and DMF (0.5ml). The resultant reaction mixture was stirred at ambient temperature under nitrogen for 30 minutes. A second Solution A was prepared and added to the reaction mixture. The resultant reaction mixture was stirred at ambient temperature for a further 15 minutes and the reaction mixture was evaporated in a centrifugal evaporator. The residue was taken into dichloromethane (1 ml) and trifluoroacetic acid (1 ml), the resultant mixture stirred at ambient temperature for 1 hour, treated with more trifluoroacetic acid (1 ml), and evaporated. The residue was dissolved in methanol (5 ml) and added to an Isolute SCX-3 cation exchange cartridge (5 g), followed by methanol (30 ml).

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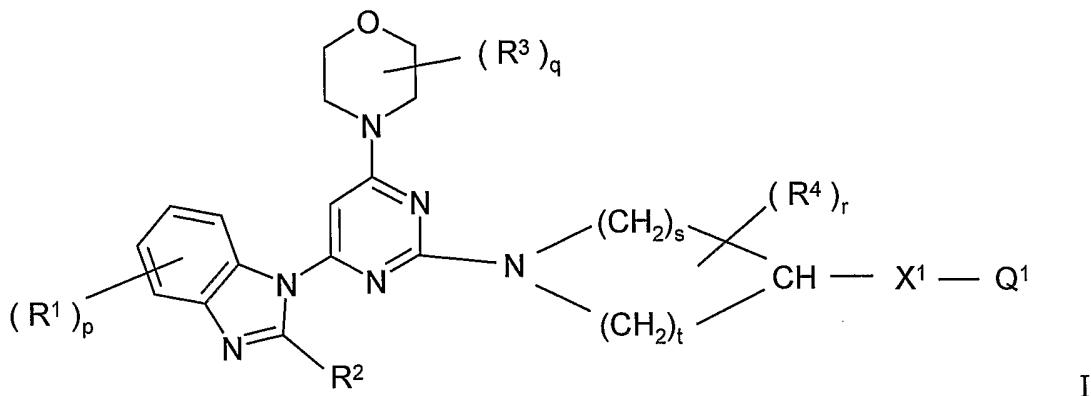
The product was then eluted by addition of a 7M solution of ammonia in methanol (15 ml) and after evaporation was further purified by HPLC using a Waters "Xbridge" preparative reversed-phase column (5 microns silica, 19 mm diameter, 100 mm length) using decreasingly polar mixtures of water [containing 1% aqueous ammonium hydroxide ($d=0.88$)] and acetonitrile as eluent. There was thus obtained the title compound (0.032 g); NMR Spectrum: (DMSO d_6) 1.25 (d, 3H), 1.37-1.43 (m, 2H), 1.56-1.64 (m, 3H), 1.77 (d, 2H), 1.77 (m, 1H), 1.91-1.96 (m, 1H), 2.77-2.83 (m, 2H), 3.04 (t, 2H), 3.08-3.26 (m, 1H), 3.45-3.49 (m, 2H), 3.61-3.65 (m, 1H), 3.74 (d, 1H), 3.84 (d, 1H), 3.94-3.97 (m, 1H), 4.13 (s, 1H), 4.41 (s, 1H), 4.49 (d, 2H), 6.33 (s, 1H), 7.40-7.47 (m, 2H), 7.50 (t, 1H), 7.75 (d, 1H), 7.81 (d, 1H), 7.87 (d, 1H). Mass Spectrum: $M+H^+$ 541.

The 1-[4-[2-(difluoromethyl)benzoimidazol-1-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]piperidin-4-amine used as a starting material was prepared as follows:-

A mixture of *tert*-butyl N-[1-[4-chloro-6-[[2-[(2,2-difluoroacetyl)amino]phenyl]amino]pyrimidin-2-yl]-4-piperidyl]carbamate (0.155 g), (3S)-3-methylmorpholine (0.157 g) and DMA (0.5 ml) was heated in a sealed vessel in a microwave at 200°C for 8 hours, cooled to ambient temperature and then evaporated. There was thus obtained *tert*-butyl N-[1-[4-[2-(difluoromethyl)benzoimidazol-1-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]-4-piperidyl]carbamate, which was used without further purification. This was taken into dichloromethane (0.5 ml) and trifluoroacetic acid (0.5 ml), stirred for 30 minutes at ambient temperature under nitrogen, treated with more trifluoroacetic acid (1 ml), and stirred at ambient temperature for a further hour. The resultant reaction mixture was stirred while sodium carbonate solution (2M, 5 ml) was added dropwise, then the organic layer was separated and the aqueous layer washed three times with dichloromethane (5 ml). The dichloromethane solutions were combined, dried over magnesium sulfate, and evaporated. The product was purified by chromatography on silica eluting with increasing amounts in dichloromethane of a 10% solution of aqueous ammonia ($d=0.88$) in methanol. There was thus obtained 1-[4-[2-(difluoromethyl)benzoimidazol-1-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]piperidin-4-amine (79% pure by LCMS method B1, 0.049 g); NMR Spectrum: (DMSO d_6) 1.11-1.22 (m, 2H), 1.25 (d, 3H), 1.76-1.77 (m, 2H), 2.94-3.05 (m, 1H), 3.16-3.30 (m, 1H), 3.45-3.51 (m, 1H), 3.61-3.65 (m, 1H), 3.74 (d, 1H), 3.93-3.97 (m, 1H), 4.10 (d, 1H), 4.40 (s, 1H), 4.46 (d, 2H), 6.30 (s, 1H), 7.40-7.49 (m, 2H), 7.52 (t, 1H), 7.75-7.80 (d, 1H), 7.87 (d, 1H). Mass Spectrum: $M+H^+$ 444.

CLAIMS

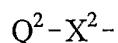
1. A pyrimidine derivative of the Formula I



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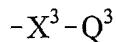
wherein **p** is 0, 1, 2 or 3;

each **R¹** group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyoxy, (1-6C)alkylthio, (1-6C)alkylsulphiny, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N,N*-di-[(1-6C)alkyl]carbamoyl, (2-6C) alkanoyl, (2-6C) alkanoyloxy, (2-6C) alkanoylamino, *N*-(1-6C) alkyl-(2-6C) alkanoylamino, (3-6C) alkenoylamino, *N*-(1-6C) alkyl-(3-6C) alkenoylamino, (3-6C) alkynoylamino, *N*-(1-6C) alkyl-(3-6C) alkynoylamino, *N'*-(1-6C) alkylureido, *N,N'*-di-[(1-6C) alkyl]ureido, *N*-(1-6C) alkylureido, *N,N'*-di-[(1-6C) alkyl]ureido, *N,N',N'*-tri-[(1-6C) alkyl]ureido, *N*-(1-6C) alkylsulphamoyl, *N,N*-di-[(1-6C) alkyl]sulphamoyl, (1-6C) alkanesulphonylamino and *N*-(1-6C) alkyl-(1-6C) alkanesulphonylamino, or from a group of the formula :

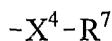


20 wherein **X²** is a direct bond or is selected from O, S, SO, SO₂, *N*(R⁵), CO, CH(OR⁵), CON(R⁵), N(R⁵)CO, N(R⁵)CON(R⁵), SO₂N(R⁵), N(R⁵)SO₂, OC(R⁵)₂, SC(R⁵)₂ and N(R⁵)C(R⁵)₂, wherein R⁵ is hydrogen or (1-8C)alkyl, and Q² is aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, (3-8C)cycloalkenyl, (3-8C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocycl or heterocycl-(1-6C)alkyl, or (R¹)_p is (1-3C)alkylenedioxy,

and wherein any CH, CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH, CH₂ or CH₃ group one or more halogeno or (1-8C)alkyl substituents and/or a substituent selected from hydroxy, mercapto, amino, cyano, carboxy, carbamoyl, ureido, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, 5 di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylureido, N'-(1-6C)alkylureido, N',N'-di-[(1-6C)alkyl]ureido, N,N'-di-[(1-6C)alkyl]ureido, N,N',N'-tri-[(1-6C)alkyl]ureido, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and 10 N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X³ is a direct bond or is selected from O, S, SO, SO₂, N(R⁶), CO, CH(OR⁶), CON(R⁶), N(R⁶)CO, N(R⁶)CON(R⁶), SO₂N(R⁶), N(R⁶)SO₂, C(R⁶)₂O, C(R⁶)₂S and C(R⁶)₂N(R⁶), wherein R⁶ is hydrogen or (1-8C)alkyl, and Q³ is aryl, aryl-(1-6C)alkyl, 15 (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, (3-8C)cycloalkenyl, (3-8C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, and wherein any aryl, (3-8C)cycloalkyl, (3-8C)cycloalkenyl, heteroaryl or heterocyclyl group within a substituent on R¹ optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, 20 carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylureido, 25 N'-(1-6C)alkylureido, N',N'-di-[(1-6C)alkyl]ureido, N,N'-di-[(1-6C)alkyl]ureido, N,N',N'-tri-[(1-6C)alkyl]ureido, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



30 wherein X⁴ is a direct bond or is selected from O and N(R⁸), wherein R⁸ is hydrogen or (1-8C)alkyl, and R⁷ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, mercapto-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, (1-6C)alkylthio-(1-6C)alkyl, cyano-(1-6C)alkyl,

amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl,

(2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl,

N-(1-6C)alkylureido-(1-6C)alkyl, *N'*-(1-6C)alkylureido-(1-6C)alkyl,

N',N'-di-[(1-6C)alkyl]ureido-(1-6C)alkyl, *N,N'*-di-[(1-6C)alkyl]ureido-(1-6C)alkyl or

5 *N,N',N'*-tri-[(1-6C)alkyl]ureido-(1-6C)alkyl, or from a group of the formula :

$$-X^5-Q^4$$

wherein X^5 is a direct bond or is selected from O, CO and N(R^9), wherein R^9 is hydrogen or (1-8C)alkyl, and Q^4 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, hydroxy, (1-8C)alkyl and (1-6C)alkoxy,

10 and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo or thioxo substituents,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, 15 $N(R^{10})$, CO, CH(OR¹⁰), CON(R^{10}), $N(R^{10})CO$, $N(R^{10})CON(R^{10})$, SO₂N(R^{10}), $N(R^{10})SO_2$, CH=CH and C≡C wherein R^{10} is hydrogen or (1-8C)alkyl;

20 R^2 is fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, hydroxy, amino, formamido, (1-6C)alkoxycarbonylamino, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-(2-6C)alkanoylamino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, hydroxy-(1-6C)alkyl or (1-6C)alkoxy-(1-6C)alkyl;

25 q is 0, 1, 2, 3 or 4;

each R^3 group, which may be the same or different, is (1-8C)alkyl or a group of the formula :

$$-X^6-R^{11}$$

25 wherein X^6 is a direct bond or is selected from O and N(R^{12}), wherein R^{12} is hydrogen or (1-8C)alkyl, and R^{11} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl or (2-6C)alkanoylamino-(1-6C)alkyl, or two R^3 groups together form a methylene, ethylene or trimethylene group;

30 r is 0, 1, 2, 3 or 4;

each R^4 group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, mercapto, amino, carboxy, carbamoyl, ureido,

(1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio,
 (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino,
 (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl, *N,N*-di-[(1-6C)alkyl]carbamoyl,
 (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, *N*-(1-6C)alkyl-
 5 (2-6C)alkanoylamino, *N'*-(1-6C)alkylureido, *N,N'*-di-[(1-6C)alkyl]ureido,
N-(1-6C)alkylureido, *N,N'*-di-[(1-6C)alkyl]ureido, *N,N',N'*-tri-[(1-6C)alkyl]ureido,
N-(1-6C)alkylsulphamoyl, *N,N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and
N-(1-6C)alkyl-(1-6C)alkanesulphonylamino,

or two R⁴ groups together form a methylene, ethylene or trimethylene group;

10 s is 1 or 2;

t is 1, 2 or 3;

X¹ is a direct bond or is selected from CO, N(R¹³)CO, CON(R¹³), N(R¹³)CON(R¹³),
 N(R¹³)COC(R¹³)₂O, N(R¹³)COC(R¹³)₂S, N(R¹³)COC(R¹³)₂N(R¹³) and
 N(R¹³)COC(R¹³)₂N(R¹³)CO, wherein R¹³ is hydrogen or (1-8C)alkyl; and

15 Q¹ is (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, halogeno-(1-6C)alkyl,
 hydroxy-(1-6C)alkyl, mercapto-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl,
 amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl,
 (1-6C)alkylthio-(1-6C)alkyl, (1-6C)alkylsulphanyl-(1-6C)alkyl,
 (1-6C)alkylsulphonyl-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl,

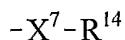
20 N-(1-6C)alkyl-(2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl,
 N-(1-6C)alkylureido-(1-6C)alkyl, *N'*-(1-6C)alkylureido-(1-6C)alkyl,
N,N'-di-[(1-6C)alkyl]ureido-(1-6C)alkyl, *N,N'*-di-[(1-6C)alkyl]ureido-(1-6C)alkyl,
N,N',N'-tri-[(1-6C)alkyl]ureido-(1-6C)alkyl, (1-6C)alkanesulphonylamino-(1-6C)alkyl or
N-(1-6C)alkyl-(1-6C)alkanesulphonylamino-(1-6C)alkyl,

25 or Q¹ is aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl,
 (3-8C)cycloalkenyl, (3-8C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl,
 heterocycl or heterocycl-(1-6C)alkyl,

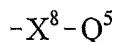
and wherein any CH, CH₂ or CH₃ group within the Q¹ group optionally bears on each
 said CH, CH₂ or CH₃ group one or more halogeno or (1-8C)alkyl substituents and/or a
 30 substituent selected from hydroxy, mercapto, amino, cyano, carboxy, carbamoyl, ureido,
 (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino,
 di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl,

N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,
N-(1-6C)alkyl-(2-6C)alkanoylamino, N'-(1-6C)alkylureido, N',N'-di-[(1-6C)alkyl]ureido,
N-(1-6C)alkylureido, N,N'-di-[(1-6C)alkyl]ureido, N,N',N'-tri-[(1-6C)alkyl]ureido,
N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and
5 *N-(1-6C)alkyl-(1-6C)alkanesulphonylamino,*

and wherein any aryl, (3-8C)cycloalkyl, (3-8C)cycloalkenyl, heteroaryl or heterocyclyl group within the Q¹ group optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy,
10 (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl,
(1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl,
(2-6C)alkanoyl, (2-6C)alkanoyloxy, *N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl,*
(2-6C)alkanoylamino, *N-(1-6C)alkyl-(2-6C)alkanoylamino, N'-(1-6C)alkylureido,*
N',N'-di-[(1-6C)alkyl]ureido, N-(1-6C)alkylureido, N,N'-di-[(1-6C)alkyl]ureido,
15 *N,N',N'-tri-[(1-6C)alkyl]ureido, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl,*
(1-6C)alkanesulphonylamino and *N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a*
group of the formula :



wherein X⁷ is a direct bond or is selected from O and N(R¹⁵), wherein R¹⁵ is hydrogen or
20 (1-8C)alkyl, and R¹⁴ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl,
cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or
di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :



wherein X⁸ is a direct bond or is selected from O, CO and N(R¹⁷), wherein R¹⁷ is hydrogen or
25 (1-8C)alkyl, and Q⁵ is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl
or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same
or different, selected from halogeno, hydroxy, (1-8C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within the Q¹ group optionally bears 1 or 2 oxo or
thioxo substituents,

30 and wherein adjacent carbon atoms in any (2-6C)alkylene chain within the Q¹ group are
optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂,

$N(R^{16})$, $N(R^{16})CO$, $CON(R^{16})$, $N(R^{16})CON(R^{16})$, CO , $CH(OR^{16})$, $N(R^{16})SO_2$, $SO_2N(R^{16})$, $CH=CH$ and $C\equiv C$ wherein R^{16} is hydrogen or (1-8C)alkyl;

and wherein the 5-position on the pyrimidine ring may optionally bear a (1-8C)alkyl group;

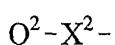
5 or a pharmaceutically-acceptable salt thereof.

2. A pyrimidine derivative of the Formula I according to claim 1 wherein :-

p is 0, 1, 2 or 3;

each R^1 group, which may be the same or different, is selected from halogeno,

10 trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N -(1-6C)alkylcarbamoyl, N,N -di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N -(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino, N -(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino, N -(1-6C)alkyl-(3-6C)alkynoylamino, N' -(1-6C)alkylureido, N',N' -di-[(1-6C)alkyl]ureido, N -(1-6C)alkylureido, N,N' -di-[(1-6C)alkyl]ureido, N,N',N' -tri-[(1-6C)alkyl]ureido, N -(1-6C)alkylsulphamoyl, N,N -di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N -(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X^2 is a direct bond or is selected from O, S, SO, SO_2 , $N(R^5)$, CO, $CH(OR^5)$, $CON(R^5)$, $N(R^5)CO$, $N(R^5)CON(R^5)$, $SO_2N(R^5)$, $N(R^5)SO_2$, $OC(R^5)_2$, $SC(R^5)_2$ and $N(R^5)C(R^5)_2$, wherein R^5 is hydrogen or (1-8C)alkyl, and Q^2 is aryl, aryl-(1-6C)alkyl,

25 (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, (3-8C)cycloalkenyl, (3-8C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or $(R^1)_p$ is (1-3C)alkylenedioxy,

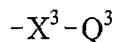
and wherein any CH, CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH, CH_2 or CH_3 group one or more halogeno or (1-8C)alkyl substituents and/or a

30 substituent selected from hydroxy, mercapto, amino, cyano, carboxy, carbamoyl, ureido, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N -(1-6C)alkylcarbamoyl,

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N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylureido, N'-(1-6C)alkylureido, N',N'-di-[(1-6C)alkyl]ureido, N,N',N'-tri-[(1-6C)alkyl]ureido, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and

5 *N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :*

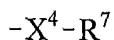


wherein X^3 is a direct bond or is selected from O, S, SO, SO₂, N(R⁶), CO, CH(OR⁶), CON(R⁶), N(R⁶)CO, N(R⁶)CON(R⁶), SO₂N(R⁶), N(R⁶)SO₂, C(R⁶)₂O, C(R⁶)₂S and C(R⁶)₂N(R⁶), wherein R⁶ is hydrogen or (1-8C)alkyl, and Q³ is aryl, aryl-(1-6C)alkyl,

10 (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, (3-8C)cycloalkenyl, (3-8C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, and wherein any aryl, (3-8C)cycloalkyl, (3-8C)cycloalkenyl, heteroaryl or heterocyclyl group within a substituent on R¹ optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy,

15 carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyoxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylureido,

20 N'-(1-6C)alkylureido, N',N'-di-[(1-6C)alkyl]ureido, N,N'-di-[(1-6C)alkyl]ureido, N,N',N'-tri-[(1-6C)alkyl]ureido, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



25 wherein X^4 is a direct bond or is selected from O and N(R⁸), wherein R⁸ is hydrogen or (1-8C)alkyl, and R⁷ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, mercapto-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, (1-6C)alkylthio-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl, N-(1-6C)alkylureido-(1-6C)alkyl, N'-(1-6C)alkylureido-(1-6C)alkyl, N',N'-di-[(1-6C)alkyl]ureido-(1-6C)alkyl or N,N',N'-tri-[(1-6C)alkyl]ureido-(1-6C)alkyl, or from a group of the formula :

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$-X^5-Q^4$

wherein X^5 is a direct bond or is selected from O, CO and N(R^9), wherein R^9 is hydrogen or (1-8C)alkyl, and Q^4 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, hydroxy, (1-8C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 oxo or thioxo substituents,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R^{10}), CO, CH(OR¹⁰), CON(R^{10}), N(R^{10})CO, N(R^{10})CON(R^{10}), SO₂N(R^{10}), N(R^{10})SO₂, CH=CH and C≡C wherein R^{10} is hydrogen or (1-8C)alkyl;

R^2 is fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, hydroxy, amino, formamido, (1-6C)alkoxycarbonylamino, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, hydroxy-(1-6C)alkyl or (1-6C)alkoxy-(1-6C)alkyl;

q is 0, 1, 2, 3 or 4;

each R^3 group, which may be the same or different, is (1-8C)alkyl or a group of the formula :

$-X^6-R^{11}$

wherein X^6 is a direct bond or is selected from O and N(R^{12}), wherein R^{12} is hydrogen or (1-8C)alkyl, and R^{11} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl or (2-6C)alkanoylamino-(1-6C)alkyl, or two R^3 groups together form a methylene, ethylene or trimethylene group;

r is 0, 1, 2, 3 or 4;

each R^4 group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, mercapto, amino, carboxy, carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N'-(1-6C)alkylureido, N',N'-di-[(1-6C)alkyl]ureido,

N-(1-6C)alkylureido, *N,N'*-di-[(1-6C)alkyl]ureido, *N,N',N'*-tri-[(1-6C)alkyl]ureido,
N-(1-6C)alkylsulphamoyl, *N,N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and
N-(1-6C)alkyl-(1-6C)alkanesulphonylamino,

or two R⁴ groups together form a methylene, ethylene or trimethylene group;

5 s is 1 or 2;

t is 1, 2 or 3;

X¹ is selected from CO, N(R¹³)CO, CON(R¹³), N(R¹³)CON(R¹³), N(R¹³)COC(R¹³)₂O,
 N(R¹³)COC(R¹³)₂S, N(R¹³)COC(R¹³)₂N(R¹³) and N(R¹³)COC(R¹³)₂N(R¹³)CO, wherein R¹³ is
 hydrogen or (1-8C)alkyl; and

10 Q¹ is (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, halogeno-(1-6C)alkyl,
 hydroxy-(1-6C)alkyl, mercapto-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl,
 amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl,
 (1-6C)alkylthio-(1-6C)alkyl, (1-6C)alkylsulphinyl-(1-6C)alkyl,
 (1-6C)alkylsulphonyl-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl,

15 *N*-(1-6C)alkyl-(2-6C)alkanoylamino-(1-6C)alkyl, (1-6C)alkoxycarbonylamino-(1-6C)alkyl,
N-(1-6C)alkylureido-(1-6C)alkyl, *N'*-(1-6C)alkylureido-(1-6C)alkyl,
N,N'-di-[(1-6C)alkyl]ureido-(1-6C)alkyl, *N,N'*-tri-[(1-6C)alkyl]ureido-(1-6C)alkyl, (1-6C)alkanesulphonylamino-(1-6C)alkyl or
N-(1-6C)alkyl-(1-6C)alkanesulphonylamino-(1-6C)alkyl,

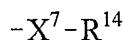
20 or Q¹ is aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl,
 (3-8C)cycloalkenyl, (3-8C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl,
 heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH, CH₂ or CH₃ group within the Q¹ group optionally bears on each
 said CH, CH₂ or CH₃ group one or more halogeno or (1-8C)alkyl substituents and/or a
 25 substituent selected from hydroxy, mercapto, amino, cyano, carboxy, carbamoyl, ureido,
 (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino,
 di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, *N*-(1-6C)alkylcarbamoyl,
N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,
N-(1-6C)alkyl-(2-6C)alkanoylamino, *N'*-(1-6C)alkylureido, *N',N'*-di-[(1-6C)alkyl]ureido,
 30 *N*-(1-6C)alkylureido, *N,N'*-di-[(1-6C)alkyl]ureido, *N,N',N'*-tri-[(1-6C)alkyl]ureido,
N-(1-6C)alkylsulphamoyl, *N,N*-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and
N-(1-6C)alkyl-(1-6C)alkanesulphonylamino,

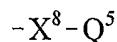
and wherein any aryl, (3-8C)cycloalkyl, (3-8C)cycloalkenyl, heteroaryl or heterocyclyl group within the Q¹ group optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy,

5 (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N'-(1-6C)alkylureido, N',N'-di-[(1-6C)alkyl]ureido, N-(1-6C)alkylureido, N,N'-di-[(1-6C)alkyl]ureido,

10 N,N',N'-tri-[(1-6C)alkyl]ureido, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X⁷ is a direct bond or is selected from O and N(R¹⁵), wherein R¹⁵ is hydrogen or (1-8C)alkyl, and R¹⁴ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :



wherein X⁸ is a direct bond or is selected from O, CO and N(R¹⁷), wherein R¹⁷ is hydrogen or (1-8C)alkyl, and Q⁵ is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, hydroxy, (1-8C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within the Q¹ group optionally bears 1 or 2 oxo or thioxo substituents,

25 and wherein adjacent carbon atoms in any (2-6C)alkylene chain within the Q¹ group are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R¹⁶), N(R¹⁶)CO, CON(R¹⁶), N(R¹⁶)CON(R¹⁶), CO, CH(OR¹⁶), N(R¹⁶)SO₂, SO₂N(R¹⁶), CH=CH and C≡C wherein R¹⁶ is hydrogen or (1-8C)alkyl;

and wherein the 5-position on the pyrimidine ring may optionally bear a (1-8C)alkyl group;

30 or a pharmaceutically-acceptable salt thereof.

3. A pyrimidine derivative of the Formula I according to claim 1 or 2 wherein :-

p is 0 or p is 1 and the R¹ group is located at the 4-, 5- or 6-position on the benzimidazolyl group and is selected from fluoro, chloro, hydroxy, amino, methoxy, ethoxy, methylamino, ethylamino and acetamido;

5 R² is fluoromethyl, difluoromethyl, trifluoromethyl, hydroxy, amino, formamido or acetamido;

q is 0 or q is 1 or 2 and each R³ group is methyl;

r is 0, or r is 1, 2, 3 or 4 and each R⁴ group, which may be the same or different, is methyl, ethyl or propyl; or r is 2 and the two R⁴ groups together form a methylene or ethylene group;

s is 2 and t is 2, or s is 1 and t is 3;

X¹ is selected from CO, NHCO, N(Me)CO, CONH and CON(Me); and

Q¹ is methyl, ethyl, propyl, isopropyl, butyl, pentyl, allyl, 2-methoxyethyl, 3-methoxypropyl, 2-ethoxyethyl, 3-ethoxypropyl, cyanomethyl, 2-cyanoethyl, 3-cyanopropyl,

15 1-cyano-1-methylethyl, 4-cyanobutyl, 5-cyanopentyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, 5-aminopentyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, 5-methylaminopentyl, ethylaminomethyl, 2-ethylaminoethyl, 3-ethylaminopropyl, 4-ethylaminobutyl, 5-ethylaminopentyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 4-dimethylaminobutyl,

20 5-dimethylaminopentyl, diethylaminomethyl, 2-diethylaminoethyl, 3-diethylaminopropyl, 4-diethylaminobutyl, 5-diethylaminopentyl, 2-methylsulphonylethyl or acetamidomethyl, or Q¹ is phenyl, benzyl, 2-phenylethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl,

25 tetrazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, furylmethyl, thienylmethyl, oxazolylmethyl, isoxazolylmethyl, imidazolylmethyl, 2-imidazolylethyl, pyrazolylmethyl, thiazolylmethyl, triazolylmethyl, oxadiazolylmethyl, thiadiazolylmethyl, tetrazolylmethyl, pyridylmethyl, 2-pyridylethyl, pyrazinylmethyl, 2-pyrazinylethyl, pyridazinylmethyl, 2-pyridazinylethyl, pyrimidinylmethyl, 2-pyrimidinylethyl, tetrahydrofuranyl,

30 tetrahydropyranyl, tetrahydrothiopyranyl, azetidinyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, indolinyl, isoindolinyl, tetrahydrofuranylmethyl, tetrahydropyranylmethyl,

1,3-dioxolanyl methyl, 1,4-dioxanyl methyl, pyrrolidinyl methyl, 2-(pyrrolidinyl)ethyl,
morpholinyl methyl, 2-(morpholinyl)ethyl, piperidinyl methyl, 2-(piperidinyl)ethyl,
homopiperidinyl methyl, piperazinyl methyl, 2-(piperazinyl)ethyl or homopiperazinyl methyl,
and wherein any CH, CH₂ or CH₃ group within the Q¹ group optionally bears on each
5 said CH, CH₂ or CH₃ group a substituent selected from hydroxy, amino, cyano, carbamoyl,
methoxy, ethoxy, methylsulphonyl, methylamino, dimethylamino, methoxycarbonyl,
ethoxycarbonyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-isopropylcarbamoyl,
N,N-dimethylcarbamoyl, acetyl, propionyl, pivaloyl, acetamido and N-methylacetamido,
and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the Q¹
10 group optionally bears 1 or 2 substituents, which may be the same or different, selected from
fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, methoxy, methylamino
and dimethylamino and any such aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group
within the Q¹ group optionally bears a substituent selected from hydroxymethyl,
methoxymethyl, cyanomethyl, aminomethyl, methylaminomethyl and dimethylaminomethyl;
15 and the 5-position on the pyrimidine ring is unsubstituted;
or a pharmaceutically-acceptable salt thereof.

4. A pyrimidine derivative of the Formula I according to claim 1 or 2 wherein :-

p is 0 or p is 1 and the R¹ group is located at the 4-, 5- or 6-position on the

20 benzimidazolyl group and is selected from fluoro, chloro, hydroxy, amino, methoxy, ethoxy,
methylamino, ethylamino and acetamido;

R² is fluoromethyl, difluoromethyl, trifluoromethyl, hydroxy, amino, formamido or
acetamido;

q is 0 or q is 1 or 2 and each R³ group is methyl;

25 r is 0, or r is 1, 2, 3 or 4 and each R⁴ group, which may be the same or different, is
methyl, ethyl or propyl; or r is 2 and the two R⁴ groups together form a methylene or ethylene
group;

s is 2 and t is 2, or s is 1 and t is 3; and

the X¹-Q¹ group is selected from glycylamino, sarcosylamino,

30 (N,N-dimethylglycyl)amino, glycylglycylamino, L-alanyl amine, 2-methylalanyl amine,
(N-methylalanyl)amino, (2S)-2-aminobutanoylamino, L-valyl amine,
(N-methyl-L-valyl)amino, 2-aminopent-4-ynoylamino, 2-aminopentanoylamino,

L-isoleucylamino, L-leucylamino, 2-methyl-L-leucylamino, (*N*-methyl-L-leucyl)amino, serylamino, (*O*-methyl-L-seryl)amino, (*N*-methyl-L-seryl)amino,

(*O*-methyl-L-homoseryl)amino, L-threonylamino, (*S*-methyl-L-cysteinyl)amino,

(*S*-methyl-L-homocysteinyl)amino, L-methionylamino, (*N*-methyl-L-lysyl)amino,

- 5 (*N*-methyl-L-ornithyl)amino, D-asparaginylamino, D-glutaminylamino, L-tyrosylamino, prolylamino and histidylamino;

and the 5-position on the pyrimidine ring is unsubstituted;

or a pharmaceutically-acceptable salt thereof.

- 10 5. A pyrimidine derivative of the Formula I according to claim 1 or 2 wherein :-

p is 0 or p is 1 and the R¹ group is located at the 4-position on the benzimidazolyl group and is selected from hydroxy and methoxy;

R² is difluoromethyl;

q is 0;

- 15 r is 0, or r is 1 or 2 and each R⁴ group is methyl, or r is 2 and the two R⁴ groups together form a methylene or ethylene group;

s is 2 and t is 2, or s is 1 and t is 3;

X¹ is CONH or CON(Me); and

Q¹ is methyl, ethyl, propyl, isopropyl, hydroxymethyl, 2-hydroxyethyl,

- 20 2-hydroxy-2-methylethyl, 1-hydroxy-1-methylethyl, 1-hydroxy-1-trifluoromethylethyl, methoxymethyl, 2-methoxyethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, methylsulphonylmethyl, 2-methylsulphonylethyl, methoxycarbonylmethyl, *tert*-butoxycarbonylmethyl, *N*-methylcarbamoylmethyl, *N*-ethylcarbamoylmethyl, *N*-isopropylcarbamoylmethyl, *N,N*-dimethylcarbamoylmethyl,

- 25 2-(*N,N*-dimethylcarbamoyl)ethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-hydroxycycloprop-1-yl, tetrahydrofuran-3-yl, tetrahydropyran-4-yl, morpholin-2-yl, morpholin-3-yl, tetrahydro-1,4-thiazin-3-yl, azetidin-2-yl, pyrrolidin-2-yl, 5-aminopyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, *N*-methylpiperidin-3-yl, piperidin-4-yl, *N*-methylpiperidin-4-yl, piperazin-1-yl, 4-methylpiperazin-1-yl, 2-oxo-1,3-thiazolidin-4-yl, 30 6-oxo-1,4,5,6-tetrahydropyridazin-3-yl, tetrahydrofuran-2-ylmethyl, tetrahydrofuran-3-ylmethyl, tetrahydropyran-4-ylmethyl, pyrrolidin-2-ylmethyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl, piperazin-1-ylmethyl,

2-oxo-1,3-oxazolidin-3-ylmethyl, 2-oxo-1,2-dihdropyridin-1-ylmethyl, phenyl,
2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-carbamoylphenyl, 3-aminomethylphenyl,
4-aminomethylphenyl, benzyl, 2-aminobenzyl, 3-aminobenzyl, 4-aminobenzyl,
3-hydroxybenzyl, 4-mesylbenzyl, 1-formamido-1-phenylethyl, 2-phenylethyl, 3-phenylpropyl,
5 3-(4-methoxyphenyl)propyl, 1-hydroxy-3-phenylpropyl, 2-furyl, 3-furyl, 3-methylfuran-2-yl,
5-methylfuran-3-yl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 2-imidazolyl, *N*-methylimidazol-2-yl,
3-pyrazolyl, 1-methyl-1*H*-pyrazol-3-yl, 4-pyrazolyl, 2-oxazolyl, 4-oxazolyl,
2-methyloxazol-4-yl, 5-oxazolyl, 3-isoxazolyl, 5-methylisoxazol-3-yl, 4-isoxazolyl,
3-methylisoxazol-4-yl, 5-methylisoxazol-4-yl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl,
10 5-thiazolyl, 4-methylthiazol-5-yl, 1*H*-1,2,3-triazol-5-yl, 4*H*-1,2,4-triazol-3-yl,
3-amino-1*H*-1,2,4-triazol-5-yl, 5-hydroxy-4*H*-1,2,4-triazol-3-yl, 1,2,3-thiadiazol-4-yl,
2,1,3-thiadiazol-4-yl, 5-tetrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 4-pyridazinyl, 2-pyrazinyl,
3-aminopyrazin-2-yl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl,
2-hydroxy-4-methylpyrimidin-5-yl, 3-thienylmethyl, 2-imidazolylmethyl, 4-imidazolylmethyl,
15 5-methyl-1*H*-imidazol-4-ylmethyl, 1*H*-pyrazol-1-ylmethyl, 1*H*-pyrazol-3-ylmethyl,
3,5-dimethyl-1*H*-pyrazol-1-ylmethyl, 4-oxazolylmethyl, 3-isoxazolylmethyl,
5-methylisoxazol-3-ylmethyl, 5-isoxazolylmethyl, 1*H*-1,2,4-triazol-1-ylmethyl,
1*H*-tetrazol-1-ylmethyl, 1*H*-tetrazol-5-ylmethyl, 2-(1*H*-pyrazol-1-yl)ethyl,
2-(3-methyl-1*H*-pyrazol-1-yl)ethyl, 2-(1*H*-1,2,4-triazol-1-yl)ethyl, 2-pyridylmethyl,
20 3-pyridylmethyl, 4-pyridylmethyl, 4-pyridazinylmethyl, 4-pyrimidinylmethyl,
2-pyrazinylmethyl, 2-pyridin-3-ylethyl, 2-pyrimidin-4-ylethyl or 2-pyridazin-4-ylethyl;
and the 5-position on the pyrimidine ring is unsubstituted;
or a pharmaceutically-acceptable salt thereof.

- 25 6. A pyrimidine derivative of the Formula I according to claim 1 or 2 wherein :-
p is 0 or p is 1 and the R¹ group is located at the 4-position on the benzimidazolyl group
and is selected from hydroxy and methoxy;
R² is difluoromethyl;
q is 0;
30 r is 0, or r is 1 or 2 and each R⁴ group is methyl, or r is 2 and the two R⁴ groups together
form a methylene or ethylene group;
s is 2 and t is 2, or s is 1 and t is 3;

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X¹ is CO; and

Q¹ is methyl, ethyl, isopropyl, hydroxymethyl, 2-hydroxy-2-methylethyl, methoxymethyl, cyclopropyl, 1-hydroxycycloprop-1-yl, tetrahydropyran-4-yl, azetidin-1-yl, azetidin-2-yl, pyrrolidin-1-yl, 3-dimethylaminopyrrolidin-1-yl, 2-carbamoylpyrrolidin-1-yl,
5 2-(2-methoxyethyl)pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, morpholin-2-yl, morpholin-3-yl, tetrahydro-1,4-thiazin-4-yl, tetrahydro-1,4-thiazin-3-yl, piperidino, 4-aminopiperidino, 3-fluoropiperidino, 4-fluoropiperidino, 3-cyanomethylpiperidino, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, 3-oxopiperazin-1-yl, tetrahydropyran-4-ylmethyl, pyrrolidin-2-ylmethyl, piperidin-3-ylmethyl, 10 piperazin-1-ylmethyl, phenyl, 3-carbamoylphenyl, 3-aminomethylphenyl, 4-aminomethylphenyl, 3-hydroxybenzyl, 2-furyl, 2-thienyl, 2-pyrrolyl, N-methylimidazol-2-yl, 3-pyrazolyl, 1-methyl-1*H*-pyrazol-3-yl, 4-pyrazolyl, 2-methyloxazol-4-yl, 5-isoxazolyl, 1*H*-1,2,3-triazol-5-yl, 1,2,3-thiadiazol-4-yl, 3-pyridyl, 4-pyridazinyl, 3-thienylmethyl, 1*H*-1,2,4-triazol-1-ylmethyl, 1*H*-tetrazol-1-ylmethyl, 1*H*-tetrazol-5-ylmethyl, 15 2-pyridin-3-ylethyl or 2-pyridazin-4-ylethyl;
and the 5-position on the pyrimidine ring is unsubstituted;
or a pharmaceutically-acceptable salt thereof.

7. A pyrimidine derivative of the Formula I according to claim 1 or 2 wherein :-

20 p is 0 or p is 1 and the R¹ group is located at the 4-position on the benzimidazolyl group and is selected from hydroxy and methoxy;

R² is difluoromethyl;

q is 0;

r is 0, or r is 1 or 2 and each R⁴ group is methyl;

25 s is 2 and t is 2, or s is 1 and t is 3;

X¹ is CO; and

Q¹ is pyrrolidin-1-yl, 3-dimethylaminopyrrolidin-1-yl, 2-carbamoylpyrrolidin-1-yl, morpholino, tetrahydro-1,4-thiazin-4-yl, piperidino, 4-aminopiperidino, 4-fluoropiperidino, 3-cyanomethylpiperidino, piperazin-1-yl or 3-oxopiperazin-1-yl;

30 and the 5-position on the pyrimidine ring is unsubstituted;
or a pharmaceutically-acceptable salt thereof.

8. A pyrimidine derivative of the Formula I according to claim 1 or 2 wherein :-

p is 0 or p is 1 and the R¹ group is located at the 4-position on the benzimidazolyl group and is selected from hydroxy and methoxy;

R² is difluoromethyl;

5 q is 0;

r is 0, or r is 1 or 2 and each R⁴ group is methyl;

s is 2;

t is 2;

X¹ is CONH; and

10 Q¹ is methyl, ethyl, allyl, 4-aminobutyl, N-isopropylcarbamoylmethyl, 2-aminobenzyl, 3-aminobenzyl, 4-aminobenzyl, cyclopropylmethyl, 5-methylisoxazol-3-ylmethyl, 4-pyridylmethyl, 2-pyridin-3-ylethyl, tetrahydrofuran-2-ylmethyl or piperidin-4-ylmethyl;

and the 5-position on the pyrimidine ring is unsubstituted;

or a pharmaceutically-acceptable salt thereof.

15

9. A pyrimidine derivative of the Formula I according to claim 1 wherein :-

p is 0;

R² is difluoromethyl;

q is 0 or q is 1 and the R³ group is methyl;

20 r is 0, or r is 1 or 2 and each R⁴ group, which may be the same or different, is methyl, ethyl or propyl, or r is 2 and the two R⁴ groups together form an methylene group;

s is 2 and t is 2;

X¹ is a direct bond or is selected from CO, NHCO, CONH and NHCOCH₂NHCO; and

25 Q¹ is methyl, ethyl, propyl, isopropyl, butyl, pentyl, allyl, 2-methoxyethyl, 3-methoxypropyl, 2-ethoxyethyl, 3-ethoxypropyl, cyanomethyl, 2-cyanoethyl, 3-cyanopropyl, 1-cyano-1-methylethyl, 4-cyanobutyl, 5-cyanopentyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, 5-aminopentyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, 5-methylaminopentyl, ethylaminomethyl, 2-ethylaminoethyl, 3-ethylaminopropyl, 4-ethylaminobutyl, 5-ethylaminopentyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 4-dimethylaminobutyl, 5-dimethylaminopentyl, diethylaminomethyl, 2-diethylaminoethyl, 3-diethylaminopropyl, 4-diethylaminobutyl, 5-diethylaminopentyl, 2-methylsulphonylethyl or acetamidomethyl, or

Q¹ is phenyl, benzyl, 2-phenylethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, furylmethyl, thienylmethyl, 5 oxazolylmethyl, isoxazolylmethyl, imidazolylmethyl, 2-imidazolylethyl, pyrazolylmethyl, thiazolylmethyl, triazolylmethyl, oxadiazolylmethyl, thiadiazolylmethyl, tetrazolylmethyl, pyridylmethyl, 2-pyridylethyl, pyrazinylmethyl, 2-pyrazinylethyl, pyridazinylmethyl, 2-pyridazinylethyl, pyrimidinylmethyl, 2-pyrimidinylethyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, azetidinyl, pyrrolinyl, pyrrolidinyl, morpholinyl, 10 tetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, indolinyl, isoindolinyl, tetrahydrofuranylmethyl, tetrahydropyranylmethyl, 1,3-dioxolanylmethyl, 1,4-dioxanyl methyl, pyrrolidinylmethyl, 2-(pyrrolidinyl)ethyl, morpholinylmethyl, 2-(morpholinyl)ethyl, piperidinylmethyl, 2-(piperidinyl)ethyl, homopiperidinylmethyl, piperazinylmethyl, 2-(piperazinyl)ethyl or homopiperazinylmethyl, 15 and wherein any CH, CH₂ or CH₃ group within the Q¹ group optionally bears on each said CH, CH₂ or CH₃ group a substituent selected from hydroxy, amino, cyano, carbamoyl, methoxy, ethoxy, methylsulphonyl, methylamino, dimethylamino, methoxycarbonyl, ethoxycarbonyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-isopropylcarbamoyl, N,N-dimethylcarbamoyl, acetyl, propionyl, pivaloyl, acetamido and N-methylacetamido, 20 and wherein any aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the Q¹ group optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, methoxy, methylamino and dimethylamino and any such aryl, (3-8C)cycloalkyl, heteroaryl or heterocyclyl group within the Q¹ group optionally bears a substituent selected from hydroxymethyl, 25 methoxymethyl, cyanomethyl, aminomethyl, methylaminomethyl and dimethylaminomethyl; and the 5-position on the pyrimidine ring is unsubstituted; or a pharmaceutically-acceptable salt thereof.

10. A pyrimidine derivative of the Formula I according to claim 1 wherein :-

30 p is 0;

R² is difluoromethyl;

q is 0 or q is 1 and the R³ group is methyl;

r is 0, or r is 1 or 2 and each R⁴ group, which may be the same or different, is methyl, ethyl or propyl, or r is 2 and the two R⁴ groups together form an ethylene group;

s is 2 and t is 2;

X¹ is a direct bond or is selected from CO, NHCO, CONH and NHCOCH₂NHCO; and

5 Q¹ is aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, 5-aminopentyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, 5-methylaminopentyl, ethylaminomethyl, 2-ethylaminoethyl, 3-ethylaminopropyl, 4-ethylaminobutyl, 5-ethylaminopentyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 4-dimethylaminobutyl, 5-dimethylaminopentyl, diethylaminomethyl, 2-diethylaminoethyl, 3-diethylaminopropyl, 4-diethylaminobutyl or 5-diethylaminopentyl, or

10 Q¹ is benzyl, 2-phenylethyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, azetidinyl, pyrrolinyl, pyrrolidinyl, morpholinyl, tetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, indolinyl or isoindolinyl,

and wherein any CH, CH₂ or CH₃ group within the Q¹ group optionally bears on each said CH, CH₂ or CH₃ group a substituent selected from hydroxy, amino, cyano, carbamoyl, methoxy, ethoxy, methylsulphonyl, methylamino, dimethylamino, methoxycarbonyl, ethoxycarbonyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-isopropylcarbamoyl, N,N-dimethylcarbamoyl, acetyl, propionyl, pivaloyl, acetamido and N-methylacetamido,

20 and wherein any aryl or heterocyclyl group within the Q¹ group optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, methoxy, methylamino and dimethylamino and any such aryl or heterocyclyl group within the Q¹ group optionally bears a substituent selected from hydroxymethyl, methoxymethyl, cyanomethyl, aminomethyl, methylaminomethyl and dimethylaminomethyl;

25 and the 5-position on the pyrimidine ring is unsubstituted;
or a pharmaceutically-acceptable salt thereof.

11. A pyrimidine derivative of the Formula I according to claim 1 wherein :-

p is 0;

30 R² is difluoromethyl;

q is 0 or q is 1 and the R³ group is methyl;

r is 0;

s is 2 and t is 2;

X¹ is a direct bond or is NHCO; and

Q¹ is aminomethyl, 2-aminoethyl, 2-phenylethyl, pyrrolidinyl or piperidinyl,

and wherein any CH, CH₂ or CH₃ group within the Q¹ group optionally bears on each

5 said CH, CH₂ or CH₃ group a substituent selected from methylamino and dimethylamino,

and wherein any aryl or heterocyclyl group within the Q¹ group optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, methoxy, methylamino and dimethylamino and any such aryl or heterocyclyl group within the Q¹ group optionally bears a substituent selected from hydroxymethyl, methoxymethyl, cyanomethyl, aminomethyl, methylaminomethyl and dimethylaminomethyl;

and the 5-position on the pyrimidine ring is unsubstituted;

or a pharmaceutically-acceptable salt thereof.

15 12. A pyrimidine derivative of the Formula I according to any one or more of claims 1 to 8, wherein p is 0; or a pharmaceutically-acceptable salt thereof.

13. A pyrimidine derivative of the Formula I according to any one or more of claims 1 to 4, wherein R² is difluoromethyl; or a pharmaceutically-acceptable salt thereof.

20 14. A pyrimidine derivative of the Formula I according to any one or more of claims 1 to 4, wherein q is 0 or q is 1 and R³ is methyl; or a pharmaceutically-acceptable salt thereof.

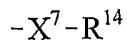
25 15. A pyrimidine derivative of the Formula I according to any one or more of claims 1 to 8, wherein r is 0; or a pharmaceutically-acceptable salt thereof.

16. A pyrimidine derivative of the Formula I according to claim 1, wherein X¹ is a direct bond or is selected from CO, N(R¹³)CO, CON(R¹³) and N(R¹³)COC(R¹³)₂N(R¹³)CO, wherein R¹³ is hydrogen or (1-2C)alkyl; or a pharmaceutically-acceptable salt thereof.

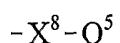
17. A pyrimidine derivative of the Formula I according to claim 1 or 16, wherein Q¹ is amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, aryl-(1-6C)alkyl or heterocyclyl,

and wherein any CH, CH₂ or CH₃ group within the Q¹ group optionally bears on each
5 said CH, CH₂ or CH₃ group one or more halogeno or (1-8C)alkyl substituents and/or a substituent selected from hydroxy, mercapto, amino, cyano, carboxy, carbamoyl, ureido, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-10 6C)alkyl-(2-6C)alkanoylamino, N'-(1-6C)alkylureido, N',N'-di-[(1-6C)alkyl]ureido, N-(1-6C)alkylureido, N,N'-di-[(1-6C)alkyl]ureido, N,N',N'-tri-[(1-6C)alkyl]ureido, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino,

and wherein any aryl or heterocyclyl group within the Q¹ group optionally bears 1, 2 or 3
15 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, ureido, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphanyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N'-(1-6C)alkylureido, N',N'-di-[(1-6C)alkyl]ureido, N-(1-6C)alkylureido, N,N'-di-[(1-6C)alkyl]ureido, N,N',N'-tri-[(1-6C)alkyl]ureido, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :



wherein X⁷ is a direct bond or is selected from O and N(R¹⁵), wherein R¹⁵ is hydrogen or (1-8C)alkyl, and R¹⁴ is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :



wherein X⁸ is a direct bond or is selected from O, CO and N(R¹⁷), wherein R¹⁷ is hydrogen or (1-8C)alkyl, and Q⁵ is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl,

heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, hydroxy, (1-8C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within the Q¹ group optionally bears 1 or 2 oxo or thioxo substituents,

5 and wherein adjacent carbon atoms in any (2-6C)alkylene chain within the Q¹ group are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R¹⁶), N(R¹⁶)CO, CON(R¹⁶), N(R¹⁶)CON(R¹⁶), CO, CH(OR¹⁶), N(R¹⁶)SO₂, SO₂N(R¹⁶), CH=CH and C≡C wherein R¹⁶ is hydrogen or (1-8C)alkyl; or a pharmaceutically-acceptable salt thereof.

10

18. A pyrimidine derivative of the Formula I selected from one or more of the following:

2-[1-[4-[2-(difluoromethyl)benzoimidazol-1-yl]-6-morpholin-4-yl-pyrimidin-2-yl]-4-piperidyl]ethanamine;

15 (2S)-N-[1-[4-[2-(difluoromethyl)benzoimidazol-1-yl]-6-morpholin-4-yl-pyrimidin-2-yl]-4-piperidyl]piperidine-2-carboxamide;

(2R)-N-[1-[4-[2-(difluoromethyl)benzoimidazol-1-yl]-6-morpholin-4-yl-pyrimidin-2-yl]-4-piperidyl]-2-methylamino-3-phenyl-propanamide;

2-amino-N-[1-[4-[2-(difluoromethyl)benzoimidazol-1-yl]-6-morpholin-4-yl-pyrimidin-2-yl]-4-piperidyl]acetamide; and

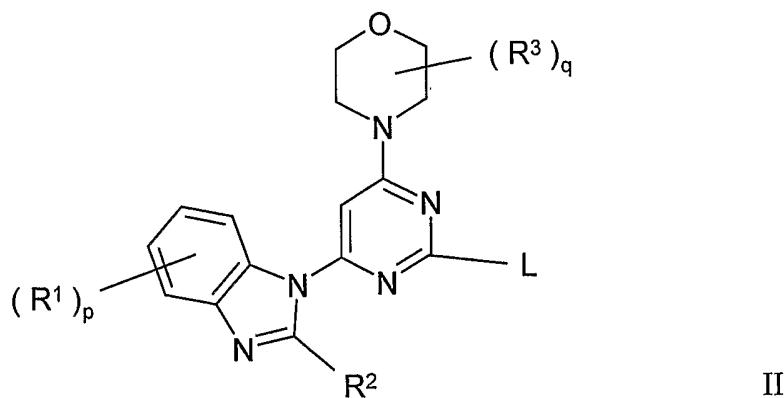
20 (2S)-N-[1-[4-[2-(difluoromethyl)-2,3-dihydrobenzoimidazol-1-yl]-6-[(3S)-3-methylmorpholin-4-yl]pyrimidin-2-yl]-4-piperidyl]pyrrolidine-2-carboxamide; or a pharmaceutically-acceptable salt thereof.

19. A process for the preparation of a pyrimidine derivative of the Formula I, or a

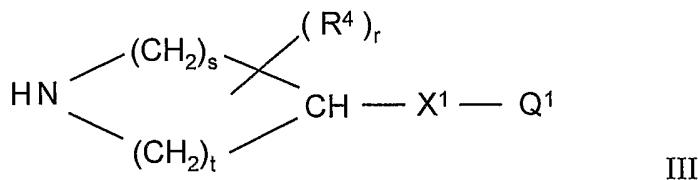
25 pharmaceutically-acceptable salt thereof, according to claim 1 which comprises :-

(a) the reaction of a pyrimidine of the Formula II

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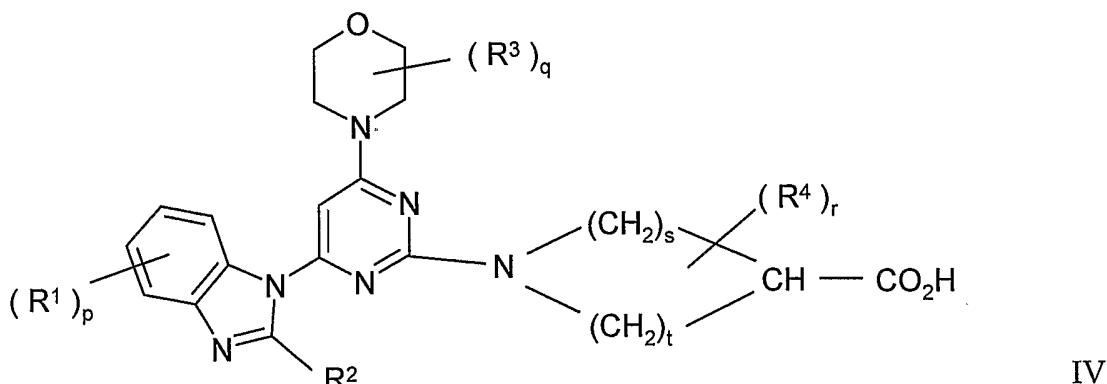


wherein L is a displaceable group and p, R¹, R², R³ and q have any of the meanings defined in claim 1 except that any functional group is protected if necessary, may be reacted with a heterocyclic compound of the Formula III



5 wherein r, R⁴, s, t, X¹ and Q¹ have any of the meanings defined in claim 1 except that any functional group is protected if necessary, whereafter any protecting group that is present is removed;

- (b) for the production of those compounds of the Formula I wherein X¹ is CON(R¹³), the
10 coupling of a carboxylic acid of the Formula IV

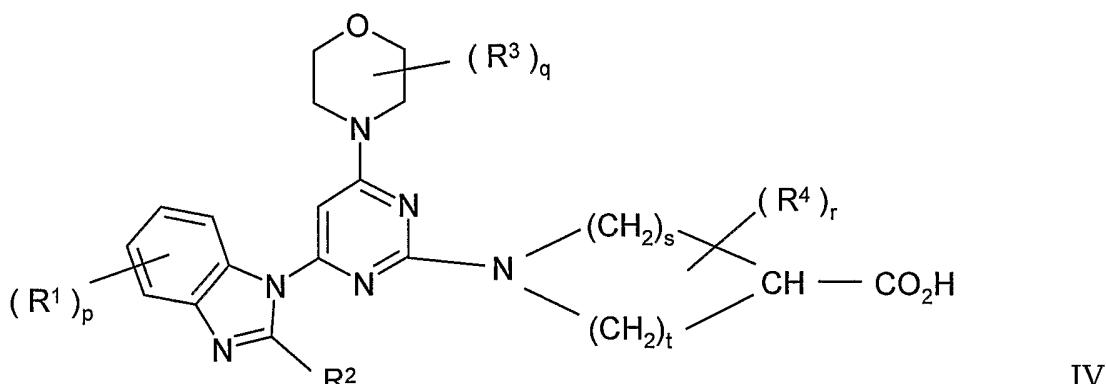


or a reactive derivative thereof, wherein p, R¹, R², q, R³, r, R⁴, s and t have any of the meanings defined in claim 1 except that any functional group is protected if necessary, with an amine of the Formula V



wherein R¹³ and Q¹ have any of the meanings defined in claim 1 except that any functional group is protected if necessary, whereafter any protecting group that is present is removed;

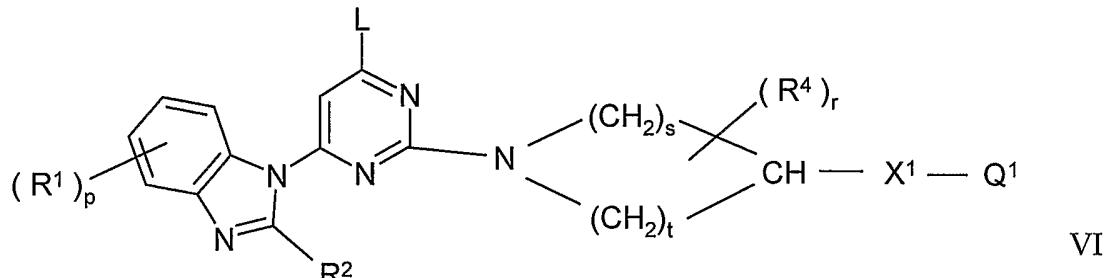
- (c) for the production of those compounds of the Formula I wherein X¹ is CO and Q¹ is a heterocyclyl group that contains an NH group, the coupling of the NH-containing heterocyclyl group where any functional group (other than the reacting NH group) is protected if necessary with a carboxylic acid of the Formula IV



or a reactive derivative thereof, wherein p, R¹, R², q, R³, r, R⁴, s and t have any of the meanings defined in claim 1 except that any functional group is protected if necessary,

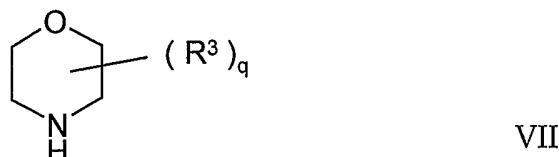
- 10 whereafter any protecting group that is present is removed;

- (d) the reaction of a pyrimidine of the Formula VI



wherein L is a displaceable group and p, R¹, R², r, R⁴, s, t, X¹ and Q¹ have any of the meanings defined in claim 1 except that any functional group is protected if necessary, with a

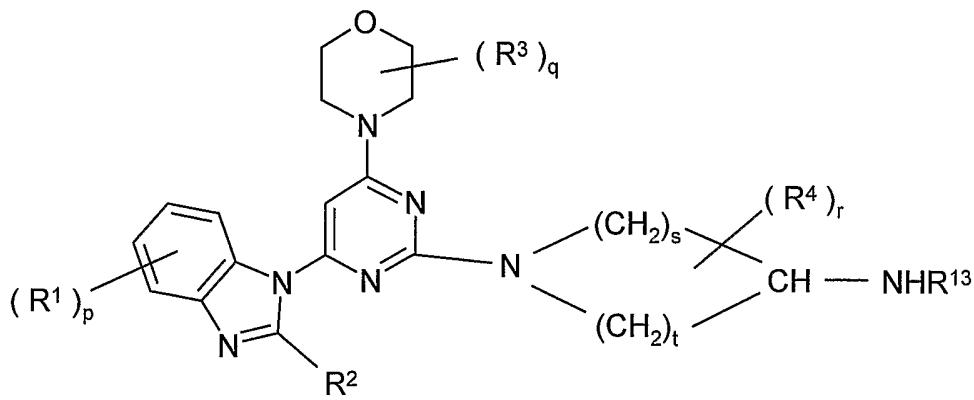
- 15 morpholine compound of the Formula VII



wherein q and R³ have any of the meanings defined in claim 1 except that any functional group is protected if necessary, whereafter any protecting group that is present is removed;

(e) for the production of those compounds of the Formula I wherein X¹ is N(R¹³)CO and Q¹ is a heterocycl1 group that contains an NH group, the coupling of phosgene, or a chemical equivalent thereof, with the NH-containing heterocycl1 group where any functional group (other than the reacting NH group) is protected if necessary and with a pyrimidine of the

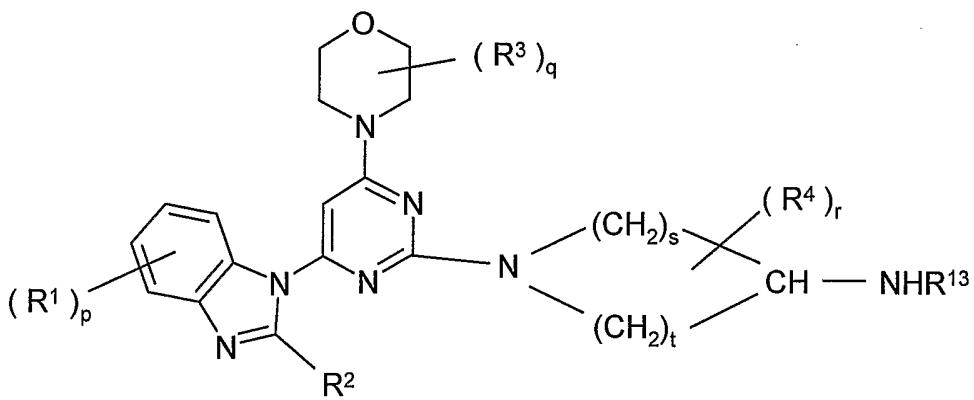
5 Formula VIII



VIII

wherein p, R¹, R², q, R³, r, R⁴, s, t and R¹³ have any of the meanings defined in claim 1 except that any functional group is protected if necessary, whereafter any protecting group that is present is removed;

10 (f) for the production of those compounds of the Formula I wherein X¹ is N(R¹³)CON(R¹³), the coupling of phosgene, or a chemical equivalent thereof, with a pyrimidine of the Formula VIII



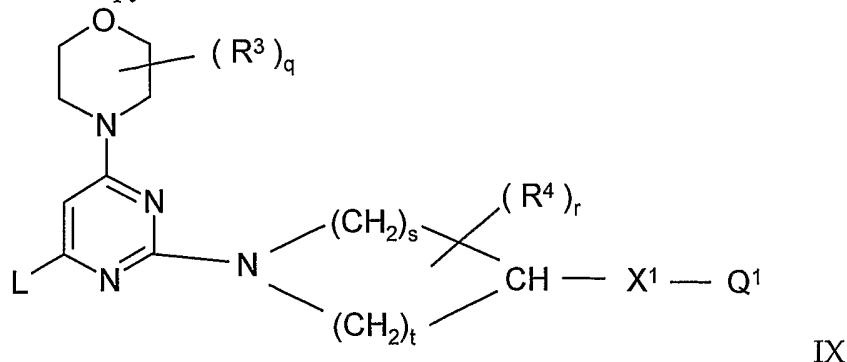
VIII

15 wherein p, R¹, R², q, R³, r, R⁴, s, t and R¹³ have any of the meanings defined in claim 1 except that any functional group is protected if necessary, and with an amine of the Formula V



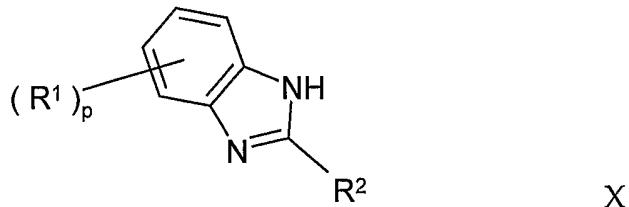
wherein R¹³ and Q¹ have any of the meanings defined in claim 1 except that any functional group is protected if necessary, whereafter any protecting group that is present is removed; or

(g) the reaction of a pyrimidine of the Formula IX



wherein L is a displaceable group and q, R³, r, R⁴, s, t, X¹ and Q¹ have any of the meanings defined in claim 1 except that any functional group is protected if necessary, with a

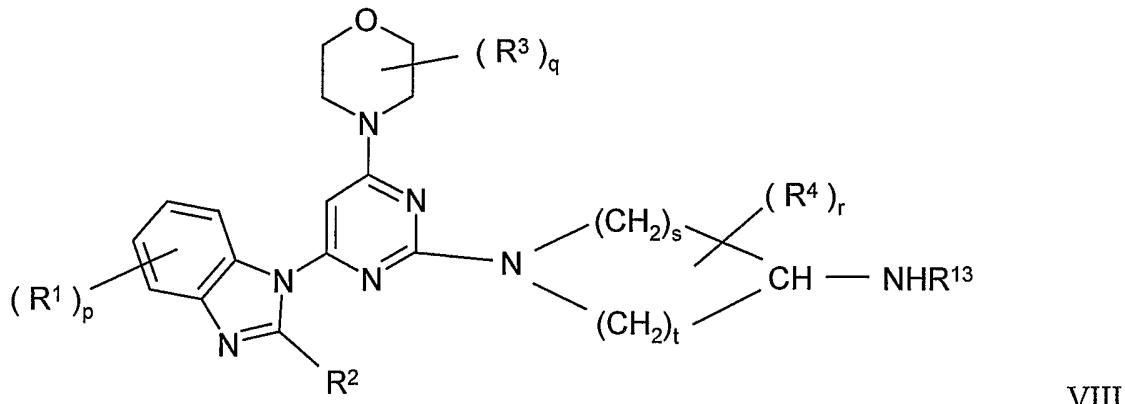
5 benzimidazole of the Formula X



wherein p, R¹ and R² have any of the meanings defined in claim 1 except that any functional group is protected if necessary, whereafter any protecting group that is present is removed;

(h) for the production of those compounds of the Formula I wherein X¹ is N(R¹³)CO or

10 N(R¹³)COC(R¹³)₂N(R¹³)CO, the coupling, conveniently in the presence of a suitable base, of a pyrimidine of the Formula VIII



wherein p, R¹, R², q, R³, r, R⁴, s, t and R¹³ have any of the meanings defined in claim 1 except that any functional group is protected if necessary, with a carboxylic acid of the formula XVII or XVII'





or a reactive derivative thereof, wherein Q¹ and R¹³ have any of the meanings defined in claim
5 1 except that any functional group is protected if necessary, whereafter any protecting group
that is present is removed;

and when a pharmaceutically-acceptable salt of a pyrimidine derivative of the Formula I
is required such as an acid-addition salt, it may be obtained by reaction of said pyrimidine
derivative with a suitable acid.

10

20. A pharmaceutical composition which comprises a pyrimidine derivative of the
Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 in association
with a pharmaceutically-acceptable diluent or carrier.

15 21. A pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof,
according to claim 1 for use as a medicament.

22. A method for producing an anti-proliferative effect in a warm-blooded animal, such as
man, in need of such treatment which comprises administering to said animal an effective
20 amount of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt
thereof, according to claim 1.

25 23. A method for producing an anti-invasive effect by the containment and/or treatment of
solid tumour disease in a warm-blooded animal, such as man, in need of such treatment which
comprises administering to said animal an effective amount of a pyrimidine derivative of the
Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1.

30 24. A method for the prevention or treatment of those tumours which are sensitive to
inhibition of PI3K enzymes and/or a mTOR kinase that are involved in the signal transduction
steps which lead to the proliferation, survival, invasiveness and migratory ability of tumour
cells which comprises administering to said animal an effective amount of a pyrimidine

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derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1.

25. A method for treating cancer of the breast, colorectum, lung and prostate in a warm
5 blooded animal such as man that is in need of such treatment which comprises administering an effective amount of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1.

26. A method for treating cancer of the bile duct, bone, bladder, head and neck, kidney,
10 liver, gastrointestinal tissue, oesophagus, ovary, pancreas, skin, testes, thyroid, uterus, cervix and vulva, and of leukaemias, multiple myeloma and lymphomas in a warm blooded animal such as man that is in need of such treatment which comprises administering an effective amount of a pyrimidine derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/003423

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 A61K31/506 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2006/005918 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; PASS MARTIN [GB]) 19 January 2006 (2006-01-19) cited in the application the whole document -----	1-26
A	WO 2006/005915 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; PASS MARTIN [GB]) 19 January 2006 (2006-01-19) cited in the application the whole document -----	1-26
A	WO 2004/048365 A (CHIRON CORP [US]; NUSS JOHN M [US]; PECCHI SABINA [US]; RENHOWE PAUL A) 10 June 2004 (2004-06-10) cited in the application the whole document -----	1-26
		-/-

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search 8 November 2007	Date of mailing of the international search report 16/11/2007
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Usuelli, Ambrogio

INTERNATIONAL SEARCH REPORTInternational application No
PCT/GB2007/003423**C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 020 462 A (ZENYAKU KOGYO KK [JP]) 19 July 2000 (2000-07-19) the whole document -----	1-26
A	WO 2006/005914 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BAILEY JOHN PETER [GB];) 19 January 2006 (2006-01-19) cited in the application the whole document -----	1-26

INTERNATIONAL SEARCH REPORT

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

Although claims 22–26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2007/003423

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 2006005918	A	19-01-2006	AR AU CA EP	049712 A1 2005261555 A1 2571756 A1 1778681 A1		30-08-2006 19-01-2006 19-01-2006 02-05-2007
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WO 2006005914	A	19-01-2006	AU CA EP	2005261551 A1 2571748 A1 1768978 A1		19-01-2006 19-01-2006 04-04-2007