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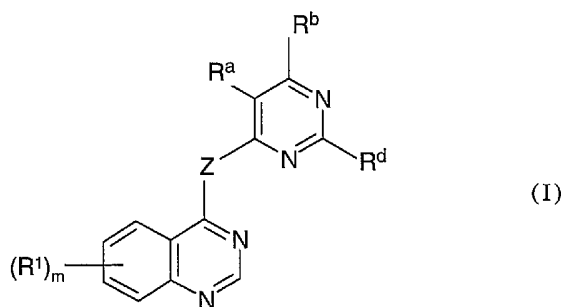
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(54) Title: 4-PYRIMIDINYL QUINAZOLINE DERIVATIVES FOR USE IN THE TREATMENT OF TUMOURS



(57) Abstract: The invention concerns quinazoline derivatives of Formula (I) wherein Z is an O, S, SO, SO<sub>2</sub>, N (R<sup>2</sup>) or C (R<sup>2</sup>)(R<sup>3</sup>) group wherein each R<sup>2</sup> or R<sup>3</sup> group is hydrogen or (1-8C) alkyl, m is 1, 2 or 3, each R<sup>1</sup> group has any of the meanings defined in the description, R<sup>a</sup> is hydrogen or halogeno, R<sup>b</sup> is hydrogen, halogeno, (1-8C) alkyl or (1-6C) alkoxy, and R<sup>d</sup> is (1-6C) alkoxy, or a pharmaceutically-acceptable salt thereof; processes for their preparation, pharmaceutical compositions containing them and their use in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

## 4-PYRIMIDINYL QUINAZOLINE DERIVATIVES FOR USE IN THE TREATMENT OF TUMOURS

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

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

15 In recent years it has been discovered that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene *i.e.* a gene which, on activation, leads to the formation of malignant tumour cells (Bradshaw, Mutagenesis, 1986, 1, 91). Several such oncogenes give rise to the production of peptides which are receptors for growth factors. Activation of the growth factor receptor complex subsequently leads to an increase in cell  
20 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<sup>v-Src</sup> tyrosine kinase (otherwise known as v-Src), and the  
25 corresponding tyrosine kinases in normal cells, for example pp60<sup>c-Src</sup> 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  
30 (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 $\alpha$ , Neu and erbB receptors, Class II receptor tyrosine kinases comprising the insulin family of receptor tyrosine kinases such as the insulin and IGF1 receptors and insulin-related receptor (IRR) and Class III receptor tyrosine kinases comprising  
5 the platelet-derived growth factor (PDGF) family of receptor tyrosine kinases such as the PDGF $\alpha$ , PDGF $\beta$  and colony-stimulating factor 1 (CSF1) receptors.

It is also known that certain tyrosine kinases belong to the class of non-receptor tyrosine kinases which are located intracellularly and are involved in the transmission of biochemical signals such as those that influence tumour cell motility, dissemination and  
10 invasiveness and subsequently metastatic tumour growth (Ullrich *et al.*, Cell, 1990, 61, 203-212, Bolen *et al.*, FASEB J., 1992, 6, 3403-3409, Brickell *et al.*, Critical Reviews in Oncogenesis, 1992, 3, 401-406, Bohlen *et al.*, Oncogene, 1993, 8, 2025-2031, Courtneidge *et al.*, Semin. Cancer Biol., 1994, 5, 239-246, Lauffenburger *et al.*, Cell, 1996, 84, 359-369, Hanks *et al.*, BioEssays, 1996, 19, 137-145, Parsons *et al.*, Current Opinion in Cell Biology,  
15 1997, 9, 187-192, Brown *et al.*, Biochimica et Biophysica Acta, 1996, 1287, 121-149 and Schlaepfer *et al.*, Progress in Biophysics and Molecular Biology, 1999, 71, 435-478). Various classes of non-receptor tyrosine kinases are known including the Src family such as the Src, Lyn and Yes tyrosine kinases, the Abl family such as Abl and Arg and the Jak family such as Jak 1 and Tyk 2.

20 It is known that the Src family of non-receptor tyrosine kinases is highly regulated in normal cells and in the absence of extracellular stimuli such kinases are maintained in an inactive conformation. However, some Src family members, for example c-Src tyrosine kinase, are frequently significantly activated (when compared to normal cell levels) in common human cancers such as gastrointestinal cancer, for example colon, rectal and stomach cancer  
25 (Cartwright *et al.*, Proc. Natl. Acad. Sci. USA, 1990, 87, 558-562 and Mao *et al.*, Oncogene, 1997, 15, 3083-3090), and breast cancer (Muthuswamy *et al.*, Oncogene, 1995, 11, 1801-1810). The Src family of non-receptor tyrosine kinases has also been located in other common human cancers such as non-small cell lung cancers (NSCLCs) including adenocarcinomas and squamous cell cancer of the lung (Mazurenko *et al.*, European Journal of  
30 Cancer, 1992, 28, 372-7), bladder cancer (Fanning *et al.*, Cancer Research, 1992, 52, 1457-62), oesophageal cancer (Jankowski *et al.*, Gut, 1992, 33, 1033-8), cancer of the prostate, ovarian cancer (Wiener *et al.*, Clin. Cancer Research, 1999, 5, 2164-70) and pancreatic cancer

(Lutz *et al.*, Biochem. and Biophys. Res. Comm., 1998, 243, 503-8). As further human tumour tissues are tested for the Src family of non-receptor tyrosine kinases it is expected that its widespread prevalence will be established.

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

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

We have now found that surprisingly certain quinazoline derivatives possess potent anti-tumour activity. Without wishing to imply that the compounds disclosed in the present  
25 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 one or more of the non-receptor tyrosine-specific protein kinases that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells. In particular, it is believed that the compounds of the present invention provide an anti-  
30 tumour effect by way of inhibition of the Src family of non-receptor tyrosine kinases, for example by inhibition of one or more of c-Src, c-Yes and c-Fyn.

It is also known that c-Src non-receptor tyrosine kinase enzyme is involved in the control of osteoclast-driven bone resorption (Soriano *et al.*, Cell, 1991, 64, 693-702;

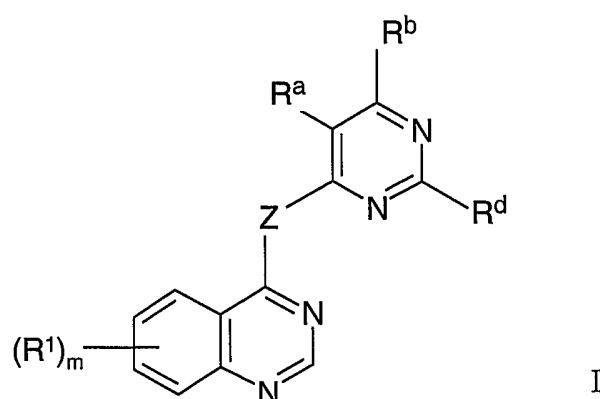
Boyce *et al.*, *J. Clin. Invest.*, 1992, 90, 1622-1627; Yoneda *et al.*, *J. Clin. Invest.*, 1993, 91, 2791-2795 and Missbach *et al.*, *Bone*, 1999, 24, 437-49). An inhibitor of c-Src non-receptor tyrosine kinase is therefore of value in the prevention and treatment of bone diseases such as osteoporosis, Paget's disease, metastatic disease in bone and tumour-induced hypercalcaemia.

5       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, hypersensitivity reactions of the skin, blood vessel diseases (for example  
10 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 the Src family of non-receptor tyrosine kinases, for example by inhibition of c-Src and/or c-Yes, whilst possessing less potent inhibitory activity against other tyrosine kinase  
15 enzymes such as the receptor tyrosine kinases, for example EGF receptor tyrosine kinase and/or VEGF receptor tyrosine kinase. Furthermore, certain compounds of the present invention possess substantially better potency against the Src family of non-receptor tyrosine kinases, for example c-Src and/or c-Yes, than against VEGF receptor tyrosine kinase. Such compounds possess sufficient potency against the Src family of non-receptor tyrosine kinases,  
20 for example c-Src and/or c-Yes, that they may be used in an amount sufficient to inhibit, for example, c-Src and/or c-Yes whilst demonstrating little activity against VEGF receptor tyrosine kinase.

      It is stated in International Patent Applications WO 02/092577, WO 02/092578 and WO 02/092579 that a range of quinazoline derivatives are useful in the treatment of cancer.  
25   The compounds are stated to possess inhibitory activity against the Src family of non-receptor tyrosine kinases. There is the disclosure therein of certain 4-substituted quinazoline derivatives including certain 4-(2-halo-5-alkoxyanilino)quinazolines. There is no disclosure therein of any 4-(pyrimidinylamino)quinazoline derivatives.

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



wherein **Z** is an O, S, SO, SO<sub>2</sub>, N(R<sup>2</sup>) or C(R<sup>2</sup>)(R<sup>3</sup>) group wherein each R<sup>2</sup> or R<sup>3</sup> group, which may be the same or different, is hydrogen or (1-8C)alkyl;

**m** is 1, 2 or 3;

5 **each R<sup>1</sup> group**, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, (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, N-(1-6C)alkylcarbamoyl, 10 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)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 :

15  $\mathbf{O}^1\text{-}\mathbf{X}^1\text{-}$

wherein  $X^1$  is a direct bond or is selected from O, S, SO,  $SO_2$ ,  $N(R^4)$ , CO,  $CH(OR^4)$ ,  $CON(R^4)$ ,  $N(R^4)CO$ ,  $SO_2N(R^4)$ ,  $N(R^4)SO_2$ ,  $OC(R^4)_2$ ,  $SC(R^4)_2$  and  $N(R^4)C(R^4)_2$ , wherein  $R^4$  is hydrogen or (1-8C)alkyl, and  $Q^1$  is aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-

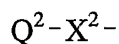
(1-6C)alkyl, (3-8C)cycloalkenyl, (3-8C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-  
20 (1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or (R<sup>1</sup>)<sub>m</sub> is (1-3C)alkylenedioxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R<sup>1</sup> substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO<sub>2</sub>, N(R<sup>5</sup>), CO, CH(OR<sup>5</sup>), CON(R<sup>5</sup>), N(R<sup>5</sup>)CO, SO<sub>2</sub>N(R<sup>5</sup>), N(R<sup>5</sup>)SO<sub>2</sub>, CH=CH and C≡C wherein R<sup>5</sup> is hydrogen or (1-8C)alkyl or, when the inserted group is N(R<sup>5</sup>), R<sup>5</sup> may also be

25 (2-6C)alkanoyl,

and wherein any  $\text{CH}_2=\text{CH}-$  or  $\text{HC}\equiv\text{C}-$  group within a  $\text{R}^1$  substituent optionally bears at the terminal  $\text{CH}_2=$  or  $\text{HC}\equiv$  position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl,  $\text{N}-(1-6\text{C})\text{alkylcarbamoyl}$ ,  $\text{N,N-di}-(1-6\text{C})\text{alkylcarbamoyl}$ , amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or

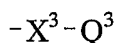
5 from a group of the formula :



wherein  $\text{X}^2$  is a direct bond or is selected from CO and  $\text{N}(\text{R}^6)\text{CO}$ , wherein  $\text{R}^6$  is hydrogen or (1-8C)alkyl, and  $\text{Q}^2$  is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

10 and wherein any  $\text{CH}_2$  or  $\text{CH}_3$  group within a  $\text{R}^1$  substituent optionally bears on each said  $\text{CH}_2$  or  $\text{CH}_3$  group one or more halogeno or (1-8C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, oxo, thioxo, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl,  $\text{N}-(1-6\text{C})\text{alkylcarbamoyl}$ ,

15  $\text{N,N-di}-(1-6\text{C})\text{alkylcarbamoyl}$ , (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,  $\text{N}-(1-6\text{C})\text{alkyl-(2-6C)alkanoylamino}$ ,  $\text{N}-(1-6\text{C})\text{alkylsulphamoyl}$ ,  $\text{N,N-di}-(1-6\text{C})\text{alkylsulphamoyl}$ , (1-6C)alkanesulphonylamino and  $\text{N}-(1-6\text{C})\text{alkyl-(1-6C)alkanesulphonylamino}$ , or from a group of the formula :

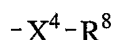


20 wherein  $\text{X}^3$  is a direct bond or is selected from O, S, SO,  $\text{SO}_2$ ,  $\text{N}(\text{R}^7)$ , CO,  $\text{CH}(\text{OR}^7)$ ,  $\text{CON}(\text{R}^7)$ ,  $\text{N}(\text{R}^7)\text{CO}$ ,  $\text{SO}_2\text{N}(\text{R}^7)$ ,  $\text{N}(\text{R}^7)\text{SO}_2$ ,  $\text{C}(\text{R}^7)_2\text{O}$ ,  $\text{C}(\text{R}^7)_2\text{S}$  and  $\text{N}(\text{R}^7)\text{C}(\text{R}^7)_2$ , wherein  $\text{R}^7$  is hydrogen or (1-8C)alkyl, and  $\text{Q}^3$  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,

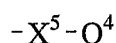
25 and wherein any aryl, heteroaryl or heterocyclyl group within a  $\text{R}^1$  substituent optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (2-6C)alkenyloxy, (2-6C)alkynyloxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino,

30 di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl,  $\text{N}-(1-6\text{C})\text{alkylcarbamoyl}$ ,  $\text{N,N-di}-(1-6\text{C})\text{alkylcarbamoyl}$ , (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,  $\text{N}-(1-6\text{C})\text{alkyl-(2-6C)alkanoylamino}$ ,  $\text{N}-(1-6\text{C})\text{alkylsulphamoyl}$ ,

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



wherein  $X^4$  is a direct bond or is selected from O and N( $R^9$ ), wherein  $R^9$  is hydrogen or (1-8C)alkyl, and  $R^8$  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, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, or from a group of the formula :



wherein  $X^5$  is a direct bond or is selected from O, N( $R^{10}$ ) and CO, wherein  $R^{10}$  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, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy,

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

$R^a$  is hydrogen or halogeno;

$R^b$  is hydrogen, halogeno, (1-8C)alkyl or (1-6C)alkoxy; and

$R^d$  is (1-6C)alkoxy; and

or a pharmaceutically-acceptable salt thereof.

In this specification the generic term “(1-8C)alkyl” includes both straight-chain and 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, cyclopentylmethyl and 2-cyclopentylethyl. However references to individual alkyl groups such as “propyl” are specific for the straight-chain version only, references to individual branched-chain alkyl groups such as “isopropyl” are specific for the branched-chain version only 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 methoxy, ethoxy, cyclopropyloxy, cyclopentyloxy, cyclopentylmethoxy and 2-cyclobutylethoxy, (1-6C)alkylamino includes methylamino, ethylamino, cyclobutylamino, cyclohexylamino and 2-cyclopropylethylamino,

and di-[(1-6alkyl)amino] includes dimethylamino, diethylamino, N-cyclobutyl-N-methylamino, N-cyclohexyl-N-ethylamino and N-cyclopentylmethyl-N-methylamino.

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

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

A suitable value for any one of the 'Q' groups ( $Q^1$  to  $Q^4$ ) 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 ( $Q^1$  or  $Q^3$ ) 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 or bicyclo[2.2.1]heptyl and a suitable value for any one of the 'Q' groups ( $Q^1$  or  $Q^3$ ) when it is (3-8C)cycloalkenyl or for the (3-8C)cycloalkenyl group within a 'Q' group is, for example, cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl.

A suitable value for any one of the 'Q' groups ( $Q^1$  to  $Q^4$ ) 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, quinoxalinyl, cinnolinyl or naphthyridinyl.

A suitable value for any one of the 'Q' groups ( $Q^1$  to  $Q^4$ ) 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, tetrahydropyranyl, oxepanyl, tetrahydrothienyl, 1,1-dioxotetrahydrothienyl, tetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, azetidiny, pyrrolinyl, pyrrolidinyl,

morpholinyl, tetrahydro-1,4-thiazinyl, 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl or tetrahydropyrimidinyl, preferably tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, morpholinyl, 1,1-dioxotetrahydro-4H-1,4-thiazinyl, piperidinyl or piperazinyl. A  
 5 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-oxopiperidinyl, 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, heteroarylmethyl, 2-heteroarylethyl and 3-heteroarylpropyl. The invention comprises  
 10 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.

In structural Formula I, it is to be understood that there is a hydrogen atom at the 2-position on the quinazoline ring. It is to be understood thereby that the R<sup>1</sup> substituents may  
 15 only be located at the 5-, 6-, 7- or 8-positions on the quinazoline ring *i.e.* that the 2-position remains unsubstituted.

Suitable values for any of the 'R' groups (R<sup>a</sup>, R<sup>b</sup>, R<sup>d</sup> and R<sup>1</sup> to R<sup>10</sup>) or for various groups within an R<sup>1</sup> substituent include:-

- |    |                            |                                                                                                       |
|----|----------------------------|-------------------------------------------------------------------------------------------------------|
|    | for halogeno               | fluoro, chloro, bromo and iodo;                                                                       |
| 20 | for (1-8C)alkyl:           | methyl, ethyl, propyl, isopropyl, <u>tert</u> -butyl, cyclobutyl, cyclopentyl 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;                                                      |
| 25 | for (2-6C)alkenyloxy:      | vinylloxy and allyloxy;                                                                               |
|    | for (2-6C)alkynyloxy:      | ethynyloxy and 2-propynyloxy;                                                                         |
|    | for (1-6C)alkylthio:       | methylthio, ethylthio and propylthio;                                                                 |
|    | for (1-6C)alkylsulphinyl:  | methylsulphinyl and ethylsulphinyl;                                                                   |
|    | for (1-6C)alkylsulphonyl:  | methylsulphonyl and ethylsulphonyl;                                                                   |
| 30 | for (1-6C)alkylamino:      | methylamino, ethylamino, propylamino, isopropylamino and butylamino;                                  |
|    | for di-[(1-6C)alkyl]amino: | dimethylamino, diethylamino, <u>N</u> -ethyl-                                                         |

- N-methylamino and diisopropylamino;
- for (1-6C)alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;
- for N-(1-6C)alkylcarbamoyl: N-methylcarbamoyl, N-ethylcarbamoyl and
- 5 N-propylcarbamoyl;
- for N,N-di-[(1-6C)alkyl]carbamoyl: N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl;
- for (2-6C)alkanoyl: acetyl, propionyl and isobutyryl;
- for (2-6C)alkanoyloxy: acetoxy and propionyloxy;
- 10 for (2-6C)alkanoylamino: acetamido and propionamido;
- for N-(1-6C)alkyl-(2-6C)alkanoylamino: N-methylacetamido and N-methylpropionamido;
- for N-(1-6C)alkylsulphamoyl: N-methylsulphamoyl and N-ethylsulphamoyl;
- for N,N-di-[(1-6C)alkyl]sulphamoyl: N,N-dimethylsulphamoyl;
- for (1-6C)alkanesulphonylamino: methanesulphonylamino and ethanesulphonylamino;
- 15 for N-(1-6C)alkyl-(1-6C)alkanesulphonylamino: N-methylmethanesulphonylamino and N-methylethanesulphonylamino;
- 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;
- 20 for N-(1-6C)alkyl-(3-6C)alkynoylamino: N-methylpropiolamido;
- for amino-(1-6C)alkyl: aminomethyl, 2-aminoethyl, 1-aminoethyl and 3-aminopropyl;
- for (1-6C)alkylamino-(1-6C)alkyl: methylaminomethyl, ethylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl,
- 25 2-ethylaminoethyl and 3-methylaminopropyl;
- for di-[(1-6C)alkyl]amino-(1-6C)alkyl: dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl and 3-dimethylaminopropyl;
- for halogeno-(1-6C)alkyl: chloromethyl, 2-fluoroethyl, 2-chloroethyl,
- 30 1-chloroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl, 3-chloropropyl, 3,3-difluoropropyl and 3,3,3-trifluoropropyl;
- for hydroxy-(1-6C)alkyl: hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and

- 3-hydroxypropyl;
- for (1-6C)alkoxy-(1-6C)alkyl: methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;
- 5 for cyano-(1-6C)alkyl: cyanomethyl, 2-cyanoethyl, 1-cyanoethyl and 3-cyanopropyl;
- for (2-6C)alkanoylamino-(1-6C)alkyl: acetamidomethyl, propionamidomethyl and 2-acetamidoethyl; and
- for (1-6C)alkoxycarbonylamino-(1-6C)alkyl: methoxycarbonylaminomethyl, 10 ethoxycarbonylaminomethyl, tert-butoxycarbonylaminomethyl and 2-methoxycarbonylaminoethyl.

A suitable value for  $(R^1)_m$  when it is a (1-3C)alkylenedioxy group or for a  $R^1$  substituent when it contains a (1-3C)alkylenedioxy group is, for example, methylenedioxy, 15 ethylenedioxy, isopropylidenedioxy or ethylenedioxy and the oxygen atoms thereof occupy adjacent ring positions.

When, as defined hereinbefore, an  $R^1$  group forms a group of the formula  $Q^1-X^1$ - and, for example,  $X^1$  is a  $OC(R^4)_2$  linking group, it is the carbon atom, not the oxygen atom, of the  $OC(R^4)_2$  linking group which is attached to the quinazoline ring and the oxygen atom is 20 attached to the  $Q^1$  group. Similarly, when, for example a  $CH_3$  group within a  $R^1$  substituent bears a group of the formula  $-X^3-Q^3$  and, for example,  $X^3$  is a  $C(R^7)_2O$  linking group, it is the carbon atom, not the oxygen atom, of the  $C(R^7)_2O$  linking group which is attached to the  $CH_3$  group and the oxygen atom is linked to the  $Q^3$  group. A similar convention applies to the attachment of the group of the formula  $Q^2-X^2$ -.

25 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,  $CON(R^5)$  or  $C\equiv C$ . For example, insertion of a  $C\equiv C$  group into the ethylene chain within a 2-morpholinoethoxy group gives rise to a 4-morpholinobut-2-ynyloxy group and, for example, insertion of a CONH group into the ethylene chain within a 3-methoxypropoxy group gives 30 rise to, for example, a 2-(2-methoxyacetamido)ethoxy group.

When, as defined hereinbefore, any  $CH_2=CH$ - or  $HC\equiv C$ - group within a  $R^1$  substituent optionally bears at the terminal  $CH_2=$  or  $HC\equiv$  position a substituent such as a group of the

formula  $Q^2-X^2$  - wherein  $X^2$  is, for example, NHCO and  $Q^2$  is a heterocyclyl-(1-6C)alkyl group, suitable  $R^1$  substituents so formed include, for example, N-[heterocyclyl-(1-6C)alkyl]carbamoylvinyl groups such as N-(2-pyrrolidin-1-ylethyl)carbamoylvinyl or N-[heterocyclyl-(1-6C)alkyl]carbamoylethynyl groups such as N-(2-pyrrolidin-1-ylethyl)carbamoylethynyl.

- When, as defined hereinbefore, any  $CH_2$  or  $CH_3$  group within a  $R^1$  substituent optionally bears on each said  $CH_2$  or  $CH_3$  group one or more halogeno or (1-8C)alkyl substituents, there are suitably 1 or 2 halogeno or (1-8C)alkyl 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  $CH_2$  or  $CH_3$  group within a  $R^1$  substituent optionally bears on each said  $CH_2$  or  $CH_3$  group a substituent as defined hereinbefore, suitable  $R^1$  substituents so formed include, for example, hydroxy-substituted heterocyclyl-(1-6C)alkoxy groups such as 2-hydroxy-3-piperidinopropoxy and 2-hydroxy-3-morpholinopropoxy, 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 heterocyclyl-(1-6C)alkylamino groups such as 2-hydroxy-3-piperidinopropylamino and 2-hydroxy-3-morpholinopropylamino, hydroxy-substituted 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, hydroxy-substituted di-[(1-6C)alkyl]amino-(2-6C)alkylamino groups such as 3-dimethylamino-2-hydroxypropylamino, hydroxy-substituted (1-6C)alkoxy groups such as 2-hydroxyethoxy, (1-6C)alkoxy-substituted (1-6C)alkoxy groups such as 2-methoxyethoxy and 3-ethoxypropoxy, (1-6C)alkylsulphonyl-substituted (1-6C)alkoxy groups such as 2-methylsulphonylethoxy and heterocyclyl-substituted (1-6C)alkylamino-(1-6C)alkyl groups such as 2-morpholinoethylaminomethyl, 2-piperazin-1-ylethylaminomethyl and 3-morpholinopropylaminomethyl.

It is to be understood that when, as defined hereinbefore, any  $CH_2$  or  $CH_3$  group within a  $R^1$  substituent optionally bears on each said  $CH_2$  or  $CH_3$  group a substituent as defined hereinbefore, such an optional substituent may be present on a  $CH_2$  or  $CH_3$  group within the hereinbefore defined substituents that may be present on an aryl, heteroaryl or heterocyclyl group within a  $R^1$  substituent. For example, if  $R^1$  includes an aryl or heteroaryl group that is

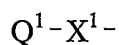
substituted by a (1-8C)alkyl group, the (1-8C)alkyl group may be optionally substituted on a CH<sub>2</sub> or CH<sub>3</sub> group therein by one of the hereinbefore defined substituents therefor. For example, if R<sup>1</sup> includes a heteroaryl group that is substituted by, for example, a (1-6C)alkylamino-(1-6C)alkyl group, the terminal CH<sub>3</sub> 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 R<sup>1</sup> group may be a heteroaryl group such as a thienyl group that is substituted by a N-(2-methylsulphonylethyl)aminomethyl group such that R<sup>1</sup> is, for example, a 5-[N-(2-methylsulphonylethyl)aminomethyl]thien-2-yl group. Further, for example, if R<sup>1</sup> 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 CH<sub>3</sub> group of the (2-6C)alkanoyl group may be further substituted by, for example, a di-[(1-6C)alkyl]amino group. For example, the R<sup>1</sup> group may be a N-(2-dimethylaminoacetyl)piperidin-4-yl group or a 4-(2-dimethylaminoacetyl)piperazin-1-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.

Particular novel compounds of the invention include, for example, quinazoline derivatives of the Formula I, or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of Z, m, R<sup>1</sup>, R<sup>a</sup>, R<sup>b</sup> and R<sup>d</sup> has any of the meanings defined hereinbefore or in paragraphs (a) to (s) hereinafter :-

- (a) Z is O, S, SO, SO<sub>2</sub>, CH<sub>2</sub> or NH;
- (b) Z is O;
- (c) Z is NH;
- (d) m is 1 or 2, and each R<sup>1</sup> group, which may be the same or different, is selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (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, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, (3-6C)alkenoylamino,

N-(1-6C)alkyl-(3-6C)alkenoylamino, (3-6C)alkynoylamino and N-(1-6C)alkyl-(3-6C)alkynoylamino, or from a group of the formula :



wherein  $X^1$  is a direct bond or is selected from O,  $N(R^4)$ ,  $CON(R^4)$ ,  $N(R^4)CO$  and  $OC(R^4)_2$

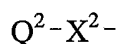
5 wherein  $R^4$  is hydrogen or (1-8C)alkyl, and  $Q^1$  is aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl-, (1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

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,  $N(R^5)$ ,  $CON(R^5)$ ,  $N(R^5)CO$ ,  $CH=CH$  and  $C\equiv C$  wherein  $R^5$  is hydrogen or (1-8C)alkyl, or, when the  
10 inserted group is  $N(R^5)$ ,  $R^5$  may also be (2-6C)alkanoyl,

and wherein any  $CH_2=CH-$  or  $HC\equiv C-$  group within a  $R^1$  substituent optionally bears at the terminal  $CH_2=$  or  $HC\equiv$  position a substituent selected from carbamoyl,

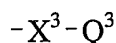
N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the

15 formula :



wherein  $X^2$  is a direct bond or is CO or  $N(R^6)CO$ , wherein  $R^6$  is hydrogen or (1-8C)alkyl, and  $Q^2$  is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

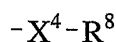
and wherein any  $CH_2$  or  $CH_3$  group within a  $R^1$  substituent optionally bears on each  
20 said  $CH_2$  or  $CH_3$  group one or more halogeno groups or a substituent selected from hydroxy, amino, oxo, (1-6C)alkoxy, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (2-6C)alkanoyloxy, (2-6C)alkanoylamino and N-(1-6C)alkyl-(2-6C)alkanoylamino, or from a group of the formula :



25 wherein  $X^3$  is a direct bond or is selected from O,  $N(R^7)$ ,  $CON(R^7)$ ,  $N(R^7)CO$  and  $C(R^7)_2O$ , wherein  $R^7$  is hydrogen or (1-8C)alkyl, and  $Q^3$  is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

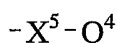
and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on  $R^1$  optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from  
30 halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylsulphonyl, N-(1-6C)alkylcarbamoyl,

N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl and (1-3C)alkylenedioxy, or optionally bears 1 substituent selected from a group of the formula :



wherein  $X^4$  is a direct bond or is selected from O and  $N(R^9)$ , wherein  $R^9$  is hydrogen or

- 5 (1-8C)alkyl, and  $R^8$  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, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, and from a group of the formula :

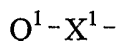


- 10 wherein  $X^5$  is a direct bond or is selected from O,  $N(R^{10})$  and CO, wherein  $R^{10}$  is hydrogen or (1-8C)alkyl, and  $Q^4$  is heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-8C)alkyl and (1-6C)alkoxy,

and wherein any heterocyclyl group within a substituent on  $R^1$  optionally bears 1 or 2

- 15 oxo substituents;

- (e) m is 1 or 2, and each  $R^1$  group, which may be the same or different, is selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, propyl, butyl, vinyl, allyl, but-3-enyl, pent-4-enyl, hex-5-enyl, ethynyl, 2-propynyl, but-3-ynyl, pent-4-ynyl, hex-5-ynyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, allyloxy, but-3-enyloxy, pent-4-enyloxy, hex-5-enyloxy, ethynyloxy, 2-propynyloxy, but-3-ynyloxy, pent-4-ynyloxy, hex-5-ynyloxy, methylamino, ethylamino, propylamino, dimethylamino, diethylamino, dipropylamino, N-methylcarbamoyl, N,N-dimethylcarbamoyl, acetamido, propionamido, acrylamido and propiolamido, or from a group of the formula :

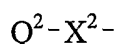


- 25 wherein  $X^1$  is a direct bond or is selected from O, NH, CONH, NHCO and  $OCH_2$  and  $Q^1$  is phenyl, benzyl, cyclopropylmethyl, 2-thienyl, 1-imidazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 2-, 3- or 4-pyridyl, 2-imidazol-1-ylethyl, 3-imidazol-1-ylpropyl, 2-(1,2,3-triazolyl)ethyl, 3-(1,2,3-triazolyl)propyl, 2-(1,2,4-triazolyl)ethyl, 3-(1,2,4-triazolyl)propyl, 2-, 3- or 4-pyridylmethyl, 2-(2-, 3- or 4-pyridyl)ethyl, 3-(2-, 3- or 4-pyridyl)propyl, tetrahydrofuran-3-yl, 3- or 4-tetrahydropyranyl, 1-, 2- or 3-pyrrolidinyl, morpholino, 1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl, piperidino, piperidin-3-yl, piperidin-4-yl, 1-, 3- or 4-homopiperidinyl, piperazin-1-yl, homopiperazin-1-yl, 1-, 2- or 3-pyrrolidinylmethyl, morpholinomethyl, piperidinomethyl,
- 30

3- or 4-piperidinylmethyl, 1-, 3- or 4-homopiperidinylmethyl, 2-pyrrolidin-1-ylethyl,  
 3-pyrrolidin-2-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-1-ylpropyl,  
 4-pyrrolidin-1-ylbutyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl,  
 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethyl, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-  
 5 4-yl)propyl, 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, 2-piperidin-3-ylethyl,  
 3-piperidin-3-ylpropyl, 2-piperidin-4-ylethyl, 3-piperidin-4-ylpropyl,  
 2-homopiperidin-1-ylethyl, 3-homopiperidin-1-ylpropyl, 2-(1,2,3,6-tetrahydropyridin-  
 1-yl)ethyl, 3-(1,2,3,6-tetrahydropyridin-1-yl)propyl, 4-(1,2,3,6-tetrahydropyridin-1-yl)butyl,  
 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl, 4-piperazin-1-ylbutyl, 2-homopiperazin-  
 10 1-ylethyl or 3-homopiperazin-1-ylpropyl,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R<sup>1</sup> substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(Me), CONH, NHCO, CH=CH and C≡C,

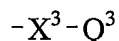
and wherein any CH<sub>2</sub>=CH- or HC≡C- group within a R<sup>1</sup> substituent optionally bears at  
 15 the terminal CH<sub>2</sub>= or HC≡ position a substituent selected from carbamoyl,  
N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N,N-dimethylcarbamoyl,  
 aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, methylaminomethyl,  
 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, dimethylaminomethyl,  
 2-dimethylaminoethyl, 3-dimethylaminopropyl or 4-dimethylaminobutyl, or from a group of  
 20 the formula :



wherein X<sup>2</sup> is a direct bond or is CO, NHCO or N(Me)CO and Q<sup>2</sup> is pyridyl, pyridylmethyl,  
 2-pyridylethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl,  
 piperidin-4-yl, piperazin-1-yl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl,  
 25 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl,  
 3-pyrrolidin-2-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl,  
 4-morpholinobutyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl,  
 4-piperidinobutyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl,  
 2-piperidin-4-ylethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or  
 30 4-piperazin-1-ylbutyl,

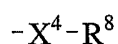
and wherein any CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on each said CH<sub>2</sub> or CH<sub>3</sub> group one or more fluoro or chloro groups or a substituent selected from

hydroxy, amino, oxo, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino, acetoxy, acetamido and N-methylacetamido or from a group of the formula :

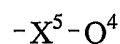


- 5 wherein  $X^3$  is a direct bond or is selected from O, NH, CONH, NHCO and  $CH_2O$  and  $Q^3$  is pyridyl, pyridylmethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, piperidin-3-ylmethyl, 2-piperidin-10 3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl,

- and wherein any aryl, heteroaryl or heterocyclyl group within a substituent on  $R^1$  optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, allyl, 2-propynyl, 15 methoxy, methylsulphonyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, acetyl, propionyl, isobutyryl, methylenedioxy, ethylidenedioxy and isopropylidenedioxy, or optionally bears 1 substituent selected from a group of the formula :



- wherein  $X^4$  is a direct bond or is selected from O and NH and  $R^8$  is 2-fluoroethyl, 20 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl, 3,3-difluoropropyl, 3,3,3-trifluoropropyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, aminomethyl, 2-aminoethyl, 3-aminopropyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-ethylaminoethyl, 3-ethylaminopropyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, acetamidomethyl, 25 methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl or tert-butoxycarbonylaminomethyl, and from a group of the formula :



- wherein  $X^5$  is a direct bond or is selected from O, NH and CO and  $Q^4$  is pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, morpholinomethyl, 30 2-morpholinoethyl, 3-morpholinopropyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, each of which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 oxo substituents;

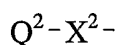
- (f) m is 1 and the R<sup>1</sup> group is located at the 5-, 6- or 7-position or m is 2 and the R<sup>1</sup> groups, which may be the same or different, are located at the 5- and 7-positions or at the 5- and 6-positions and each R<sup>1</sup> is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, vinyl, ethynyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, but-3-enyloxy, pent-4-enyloxy, hex-5-enyloxy, but-3-ynyloxy, pent-4-ynyloxy, hex-5-ynyloxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, cyclopentyloxy, cyclohexyloxy, phenoxy, benzyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, cyclopropylmethoxy, 2-imidazol-1-ylethoxy, 3-imidazol-1-ylpropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 3-(1,2,4-triazol-1-yl)propoxy, pyrid-2-ylmethoxy, pyrid-3-ylmethoxy, pyrid-4-ylmethoxy, 2-pyrid-2-ylethoxy, 2-pyrid-3-ylethoxy, 2-pyrid-4-ylethoxy, 3-pyrid-2-ylpropoxy, 3-pyrid-3-ylpropoxy, 3-pyrid-4-ylpropoxy, pyrrolidin-1-yl, morpholino, piperidino, piperazin-1-yl, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 3-piperidin-3-ylpropoxy, 2-piperidin-4-ylethoxy, 3-piperidin-4-ylpropoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 4-(1,2,3,6-tetrahydropyridin-1-yl)butoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-homopiperazin-1-ylethoxy, 3-homopiperazin-1-ylpropoxy, 2-pyrrolidin-1-ylethylamino, 3-pyrrolidin-1-ylpropylamino, 4-pyrrolidin-1-ylbutylamino, pyrrolidin-3-ylamino, pyrrolidin-2-ylmethylamino, 2-pyrrolidin-2-ylethylamino, 3-pyrrolidin-2-ylpropylamino, 2-morpholinoethylamino, 3-morpholinopropylamino, 4-morpholinobutylamino, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethylamino, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propylamino, 2-piperidinoethylamino, 3-piperidinopropylamino, 4-piperidinobutylamino, piperidin-3-ylamino, piperidin-4-ylamino, piperidin-3-ylmethylamino, 2-piperidin-3-ylethylamino, piperidin-4-ylmethylamino,

2-piperidin-4-ylethylamino, 2-homopiperidin-1-ylethylamino,  
 3-homopiperidin-1-ylpropylamino, 2-piperazin-1-ylethylamino, 3-piperazin-1-ylpropylamino,  
 4-piperazin-1-ylbutylamino, 2-homopiperazin-1-ylethylamino or  
 3-homopiperazin-1-ylpropylamino,

- 5 and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R<sup>1</sup> substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(Me), CH=CH and C≡C,

and when R<sup>1</sup> is a vinyl or ethynyl group, the R<sup>1</sup> substituent optionally bears at the terminal CH<sub>2</sub>= or HC≡ position a substituent selected from

- 10 N-(2-dimethylaminoethyl)carbamoyl, N-(3-dimethylaminopropyl)carbamoyl, methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl and 4-dimethylaminobutyl, or from a group of the formula :



- 15 wherein X<sup>2</sup> is a direct bond or is NHCO or N(Me)CO and Q<sup>2</sup> is imidazolylmethyl, 2-imidazolylethyl, 3-imidazolylpropyl, pyridylmethyl, 2-pyridylethyl, 3-pyridylpropyl, pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, piperidinomethyl,  
 20 2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, piperidin-3-ylmethyl, 2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or 4-piperazin-1-ylbutyl,

- and wherein any CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on each said CH<sub>2</sub> or CH<sub>3</sub> group one or more fluoro or chloro groups or a substituent selected from  
 25 hydroxy, oxo, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-N-propylamino, acetoxy, acetamido and N-methylacetamido,

- and wherein any phenyl, imidazolyl, triazolyl, pyridyl or heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 substituents, which may be the same or different,  
 30 selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, carbamoyl, methyl, ethyl, methoxy, ethoxy, N-methylcarbamoyl, N,N-dimethylcarbamoyl, methylenedioxy, ethylidenedioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl,

piperazin-1-yl or homopiperazin-1-yl group within a R<sup>1</sup> substituent is optionally N-substituted with allyl, 2-propynyl, methylsulphonyl, ethylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl, 3,3-difluoropropyl, 3,3,3-trifluoropropyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl,  
 5 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and  
 10 methoxy,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 oxo substituents;

(g) m is 1 and the R<sup>1</sup> group is located at the 7-position or m is 2 and the R<sup>1</sup> groups, which may be the same or different, are located at the 6- and 7-positions and each R<sup>1</sup> is selected from  
 15 hydroxy, amino, methyl, ethyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-  
 20 4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy,  
 25 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R<sup>1</sup> substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CH=CH and C≡C,

and wherein any CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on each  
 30 said CH<sub>2</sub> or CH<sub>3</sub> group one or more chloro groups or a substituent selected from hydroxy, oxo, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxy,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R<sup>1</sup> substituent is optionally N-substituted with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 oxo substituents;

- 10 (h) m is 1 and the R<sup>1</sup> group is located at the 5-position or m is 2 and the R<sup>1</sup> groups, which may be the same or different, are located at the 5- and 7-positions and each R<sup>1</sup> is selected from hydroxy, amino, methyl, ethyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 15 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, 3-piperidinyloxy, 4-piperidinyloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 20 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy, 3-homopiperazin-1-ylpropoxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R<sup>1</sup> substituent are optionally separated by the insertion into the chain of a group selected from O, NH, CH=CH and C≡C,

and wherein any CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on each said CH<sub>2</sub> or CH<sub>3</sub> group one or more chloro groups or a substituent selected from hydroxy, oxo, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, 30 N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxo,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl,

hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R<sup>1</sup> substituent is optionally N-substituted with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl,  
 5 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 oxo substituents;

- (i) m is 2 and the R<sup>1</sup> groups, which may be the same or different, are located at the 6- and 7-positions and the R<sup>1</sup> group at the 6-position is selected from hydroxy, methoxy, ethoxy and  
 10 propoxy, and the R<sup>1</sup> group at the 7-position is selected from methoxy, ethoxy, propoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-  
 15 4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and  
 20 3-homopiperazin-1-ylpropoxy,

and wherein any CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on each said CH<sub>2</sub> or CH<sub>3</sub> group one or more chloro groups or a substituent selected from hydroxy, oxo, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxo,

- 25 and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R<sup>1</sup> substituent is optionally N-substituted  
 30 with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 oxo substituents;

(j) m is 2 and the R<sup>1</sup> groups, which may be the same or different, are located at the 5- and 7-positions and the R<sup>1</sup> group at the 5-position is selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 3-piperidinyloxy, 4-piperidinyloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy, and the R<sup>1</sup> group at the 7-position is selected from hydroxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, 2-piperidin-3-ylethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein any CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on each said CH<sub>2</sub> or CH<sub>3</sub> group one or more chloro groups or a substituent selected from hydroxy, oxo, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxy,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R<sup>1</sup> substituent is optionally N-substituted with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 oxo substituents;

(k) R<sup>a</sup> is halogeno;

(l) R<sup>a</sup> is hydrogen;

(m) R<sup>a</sup> is fluoro, chloro or bromo;

(n) R<sup>a</sup> is chloro or bromo;

(o) R<sup>b</sup> is hydrogen, fluoro, chloro, bromo, methyl, ethyl, methoxy or ethoxy;

(p)  $R^b$  is hydrogen, fluoro, chloro, bromo, methoxy or ethoxy;

(q)  $R^b$  is hydrogen;

(r)  $R^d$  is methoxy or ethoxy; and

(s)  $R^d$  is methoxy.

5 Further particular novel compounds of the invention include, for example, quinazoline derivatives of the Formula I, or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of Z, m,  $R^1$ ,  $R^a$ ,  $R^b$  and  $R^d$  has any of the meanings defined hereinbefore provided that :-

(A)  $R^1$  substituents may only be located at the 5-, 6- and/or 7-positions on the quinazoline  
10 ring *i.e.* the 2- and 8-positions remain unsubstituted; or

(B)  $R^1$  substituents may only be located at the 6- and/or 7-positions on the quinazoline ring  
*i.e.* the 2-, 5- and 8-positions remain unsubstituted.

As stated hereinbefore, generally the compounds of the present invention possess potent inhibitory activity against the Src family of non-receptor tyrosine kinases, for example  
15 by inhibition of c-Src and/or c-Yes, whilst possessing less potent inhibitory activity against other tyrosine kinase enzymes such as the receptor tyrosine kinases, for example EGF receptor tyrosine kinase and/or VEGF receptor tyrosine kinase. Furthermore, certain compounds of the present invention, possess substantially better potency against the Src family of non-receptor tyrosine kinases, for example c-Src and/or c-Yes, than against EGF receptor tyrosine kinase or  
20 VEGF receptor tyrosine kinase. Such compounds possess sufficient potency against the Src family of non-receptor tyrosine kinases, for example c-Src and/or c-Yes, that they may be used in an amount sufficient to inhibit, for example, c-Src and/or c-Yes whilst demonstrating little activity against EGF receptor tyrosine kinase or VEGF receptor tyrosine kinase.

According to this aspect of the invention, there are provided quinazoline derivatives of  
25 the Formula I, or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of Z, m,  $R^1$  and  $R^b$  has any of the meanings defined hereinbefore and :-

$R^a$  is halogeno and  $R^d$  is methoxy.

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

30 Z is O or NH;

m is 1 and the R<sup>1</sup> group is located at the 5-, 6- or 7-position or m is 2 and the R<sup>1</sup> groups, which may be the same or different, are located at the 5- and 7-positions or at the 6- and 7-positions and each R<sup>1</sup> is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, vinyl, ethynyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, but-3-enyloxy, pent-4-enyloxy, hex-5-enyloxy, but-3-ynyloxy, pent-4-ynyloxy, hex-5-ynyloxy, methylamino, ethylamino, dimethylamino, diethylamino, acetamido, propionamido, cyclopentyloxy, cyclohexyloxy, phenoxy, benzyloxy, tetrahydrofuran-3-yloxy, tetrahydropyran-3-yloxy, tetrahydropyran-4-yloxy, cyclopropylmethoxy, 2-imidazol-1-ylethoxy, 3-imidazol-1-ylpropoxy, 2-(1,2,3-triazol-1-yl)ethoxy, 3-(1,2,3-triazol-1-yl)propoxy, 2-(1,2,4-triazol-1-yl)ethoxy, 3-(1,2,4-triazol-1-yl)propoxy, pyrid-2-ylmethoxy, pyrid-3-ylmethoxy, pyrid-4-ylmethoxy, 2-pyrid-2-ylethoxy, 2-pyrid-3-ylethoxy, 2-pyrid-4-ylethoxy, 3-pyrid-2-ylpropoxy, 3-pyrid-3-ylpropoxy, 3-pyrid-4-ylpropoxy, pyrrolidin-1-yl, morpholino, piperidino, piperazin-1-yl, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, 2-piperidin-3-ylethoxy, 2-piperidin-4-ylpropoxy, 3-piperidin-4-ylpropoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 4-(1,2,3,6-tetrahydropyridin-1-yl)butoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-homopiperazin-1-ylethoxy, 3-homopiperazin-1-ylpropoxy, 2-pyrrolidin-1-ylethylamino, 3-pyrrolidin-1-ylpropylamino, 4-pyrrolidin-1-ylbutylamino, pyrrolidin-3-ylamino, pyrrolidin-2-ylmethylamino, 2-pyrrolidin-2-ylethylamino, 3-pyrrolidin-2-ylpropylamino, 2-morpholinoethylamino, 3-morpholinopropylamino, 4-morpholinobutylamino, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethylamino, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propylamino, 2-piperidinoethylamino, 3-piperidinopropylamino, 4-piperidinobutylamino, piperidin-3-ylamino, piperidin-4-ylamino, piperidin-3-ylmethylamino, 2-piperidin-3-ylethylamino, piperidin-4-ylmethylamino, 2-piperidin-4-ylethylamino, 2-homopiperidin-1-ylethylamino, 3-homopiperidin-1-ylpropylamino, 2-piperazin-1-ylethylamino, 3-piperazin-1-ylpropylamino,

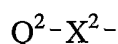
4-piperazin-1-ylbutylamino, 2-homopiperazin-1-ylethylamino or  
3-homopiperazin-1-ylpropylamino,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R<sup>1</sup> substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(Me),

5 CH=CH and C≡C,

and when R<sup>1</sup> is a vinyl or ethynyl group, the R<sup>1</sup> substituent optionally bears at the terminal CH<sub>2</sub>= or HC≡ position a substituent selected from

N-(2-dimethylaminoethyl)carbamoyl, N-(3-dimethylaminopropyl)carbamoyl,  
methylaminomethyl, 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl,  
10 dimethylaminomethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl and  
4-dimethylaminobutyl, or from a group of the formula :



wherein X<sup>2</sup> is a direct bond or is NHCO or N(Me)CO and Q<sup>2</sup> is imidazolylmethyl,

2-imidazolylethyl, 3-imidazolylpropyl, pyridylmethyl, 2-pyridylethyl, 3-pyridylpropyl,

15 pyrrolidin-1-ylmethyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 4-pyrrolidin-1-ylbutyl,  
pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, morpholinomethyl,  
2-morpholinoethyl, 3-morpholinopropyl, 4-morpholinobutyl, piperidinomethyl,  
2-piperidinoethyl, 3-piperidinopropyl, 4-piperidinobutyl, piperidin-3-ylmethyl,  
2-piperidin-3-ylethyl, piperidin-4-ylmethyl, 2-piperidin-4-ylethyl, piperazin-1-ylmethyl,  
20 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or 4-piperazin-1-ylbutyl,

and wherein any CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on each said CH<sub>2</sub> or CH<sub>3</sub> group one or more fluoro or chloro groups or a substituent selected from hydroxy, oxo, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino, N-methyl-

25 N-propylamino, acetoxy, acetamido and N-methylacetamido,

and wherein any phenyl, imidazolyl, triazolyl, pyridyl or heterocyclyl group within a substituent on R<sup>1</sup> 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, N-methylcarbamoyl, N,N-dimethylcarbamoyl, methylenedioxy,

30 ethylidenedioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R<sup>1</sup> substituent is optionally N-substituted with allyl, 2-propynyl, methylsulphonyl, ethylsulphonyl, acetyl, propionyl, isobutyryl,

2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl, 3,3-difluoropropyl, 3,3,3-trifluoropropyl, 2-methoxyethyl, 3-methoxypropyl, cyanomethyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-methylaminopropyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, 2-morpholinoethyl, 5 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2  
10 oxo substituents;

R<sup>a</sup> is hydrogen, fluoro, chloro or bromo;

R<sup>b</sup> is hydrogen, fluoro, chloro, bromo, methoxy or ethoxy; and

R<sup>d</sup> is methoxy or ethoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

15 A further particular compound of the invention is a quinazoline derivative of the Formula I wherein :

Z is NH;

m is 2 and the R<sup>1</sup> groups, which may be the same or different, are located at the 6- and 7-positions and the R<sup>1</sup> group at the 6-position is selected from hydroxy, methoxy, ethoxy and  
20 propoxy, and the R<sup>1</sup> group at the 7-position is selected from methoxy, ethoxy, propoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-  
25 4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy, piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and  
30 3-homopiperazin-1-ylpropoxy,

and wherein any CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on each said CH<sub>2</sub> or CH<sub>3</sub> group one or more chloro groups or a substituent selected from hydroxy, oxo,

amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxy,

- and wherein any heterocyclcyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R<sup>1</sup> substituent is optionally N-substituted with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,
- and wherein any heterocyclcyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 oxo substituents;

R<sup>a</sup> is hydrogen, chloro or bromo;

R<sup>b</sup> is hydrogen, fluoro, chloro, bromo, methoxy or ethoxy; and

R<sup>d</sup> is methoxy or ethoxy;

- or a pharmaceutically-acceptable acid-addition salt thereof.

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

Z is NH;

- m is 2 and the first R<sup>1</sup> group is a 6-methoxy group and the second R<sup>1</sup> group is located at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-[(3RS,4SR)-3,4-methylenedioxy-pyrrolidin-1-yl]ethoxy, 3-[(3RS,4SR)-3,4-methylenedioxy-pyrrolidin-1-yl]propoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-(4-hydroxypiperidin-1-yl)ethoxy, 3-(4-hydroxypiperidin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-(4-methylpiperazin-1-yl)butoxy, 2-(4-allylpiperazin-1-yl)ethoxy, 3-(4-allylpiperazin-1-yl)propoxy,

2-(4-prop-2-ynylpiperazin-1-yl)ethoxy, 3-(4-prop-2-ynylpiperazin-1-yl)propoxy,  
 2-(4-methylsulphonylpiperazin-1-yl)ethoxy, 3-(4-methylsulphonylpiperazin-1-yl)propoxy,  
 2-(4-acetylpiperazin-1-yl)ethoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 4-(4-acetylpiperazin-  
 1-yl)butoxy, 2-(4-isobutyrylpiperazin-1-yl)ethoxy, 3-(4-isobutyrylpiperazin-1-yl)propoxy,  
 5 4-(4-isobutyrylpiperazin-1-yl)butoxy, 2-[4-(2-fluoroethyl)piperazin-1-yl]ethoxy,  
 3-[4-(2-fluoroethyl)piperazin-1-yl]propoxy, 2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethoxy,  
 3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy,  
 3-(4-cyanomethylpiperazin-1-yl)propoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy,  
 2-chloroethoxy, 3-chloropropoxy, 4-chlorobutoxy, 2-methylsulphonylethoxy,  
 10 3-methylsulphonylpropoxy, 2-(2-methoxyethoxy)ethoxy, 2-(4-pyridyloxy)ethoxy,  
 3-pyridylmethoxy and 2-cyanopyrid-4-ylmethoxy; and

$R^a$  is chloro or bromo;

$R^b$  is hydrogen; and

$R^d$  is methoxy;

15 or a pharmaceutically-acceptable acid-addition salt thereof.

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

Z is NH;

m is 2 and the first  $R^1$  group is a 6-methoxy group and the second  $R^1$  group is located at  
 20 the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy,  
 2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy,  
 3-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]propoxy, 2-morpholinoethoxy,  
 3-morpholinopropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-(4-methylpiperazin-  
 1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-allylpiperazin-1-yl)ethoxy,  
 25 3-(4-allylpiperazin-1-yl)propoxy, 2-(4-prop-2-ynylpiperazin-1-yl)ethoxy,  
 3-(4-prop-2-ynylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy,  
 3-(4-acetylpiperazin-1-yl)propoxy, 2-(4-isobutyrylpiperazin-1-yl)ethoxy,  
 3-(4-isobutyrylpiperazin-1-yl)propoxy, 2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethoxy and  
 3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy; and

30  $R^a$  is chloro;

$R^b$  is hydrogen; and

$R^d$  is methoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

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

Z is NH;

5 m is 2 and the R<sup>1</sup> groups, which may be the same or different, are located at the 5- and 7-positions and the R<sup>1</sup> group at the 5-position is selected from methoxy, ethoxy, propoxy, isopropoxy, butoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 3-piperidinyloxy, 4-piperidinyloxy, piperidin-3-ylmethoxy, piperidin-4-ylmethoxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy, and the R<sup>1</sup> group at  
10 the 7-position is selected from hydroxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy, 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy,  
15 3-piperidinopropoxy, 4-piperidinobutoxy, 2-piperidin-3-ylethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein any CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on each  
20 said CH<sub>2</sub> or CH<sub>3</sub> group one or more chloro groups or a substituent selected from hydroxy, oxo, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxo,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl,  
25 hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R<sup>1</sup> substituent is optionally N-substituted with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

30 and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 oxo substituents;

R<sup>a</sup> is hydrogen, chloro or bromo;

$R^b$  is hydrogen, fluoro, chloro, bromo, methoxy or ethoxy; and

$R^d$  is methoxy or ethoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

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

5 Formula I wherein :

Z is NH;

m is 1 and the  $R^1$  group is located at the 5-position and is selected from ethoxy, propoxy, isopropoxy, butoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, tetrahydrothien-3-yloxy, 1,1-dioxotetrahydrothien-3-yloxy, tetrahydrothiopyran-4-yloxy, 10 1,1-dioxotetrahydrothiopyran-4-yloxy, N-methylazetidin-3-yloxy, N-ethylazetidin-3-yloxy, N-isopropylazetidin-3-yloxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 3-piperidinyloxy, N-methylpiperidin-3-yloxy, 4-piperidinyloxy, N-methylpiperidin-4-yloxy, N-allylpiperidin-4-yloxy, N-prop-2-ynylpiperidin-4-yloxy, N-acetylpiperidin-4-yloxy, N-methylsulphonylpiperidin-4-yloxy, 15 N-(2-methoxyethyl)piperidin-4-yloxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy,

or m is 2 and the first  $R^1$  group is located at the 5-position and is selected from the group of substituents listed immediately above and the second  $R^1$  group is located at the 20 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-[(3RS,4SR)-3,4-methylenedioxy-pyrrolidin-1-yl]ethoxy, 3-[(3RS,4SR)-3,4-methylenedioxy-pyrrolidin-1-yl]propoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 25 3-piperidinopropoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy, 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy, 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-4-yl)propoxy, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-(4-hydroxypiperidin-1-yl)ethoxy, 3-(4-hydroxypiperidin-1-yl)propoxy, 30 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-(4-methylpiperazin-1-yl)butoxy, 2-(4-allylpiperazin-1-yl)ethoxy, 3-(4-allylpiperazin-1-yl)propoxy,

- 2-(4-prop-2-ynylpiperazin-1-yl)ethoxy, 3-(4-prop-2-ynylpiperazin-1-yl)propoxy,  
 2-(4-methylsulphonylpiperazin-1-yl)ethoxy, 3-(4-methylsulphonylpiperazin-1-yl)propoxy,  
 2-(4-acetylpiperazin-1-yl)ethoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 4-(4-acetylpiperazin-  
 1-yl)butoxy, 2-(4-isobutyrylpiperazin-1-yl)ethoxy, 3-(4-isobutyrylpiperazin-1-yl)propoxy,  
 5 4-(4-isobutyrylpiperazin-1-yl)butoxy, 2-[4-(2-fluoroethyl)piperazin-1-yl]ethoxy,  
 3-[4-(2-fluoroethyl)piperazin-1-yl]propoxy, 2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethoxy,  
 3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy,  
 3-(4-cyanomethylpiperazin-1-yl)propoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy,  
 2-chloroethoxy, 3-chloropropoxy, 4-chlorobutoxy, 2-methylsulphonylethoxy,  
 10 3-methylsulphonylpropoxy, 2-(2-methoxyethoxy)ethoxy, 2-(4-pyridyloxy)ethoxy,  
 3-pyridylmethoxy and 2-cyanopyrid-4-ylmethoxy;

$R^a$  is hydrogen, chloro or bromo;

$R^b$  is hydrogen, chloro, bromo or methoxy; and

$R^d$  is methoxy or ethoxy;

- 15 or a pharmaceutically-acceptable acid-addition salt thereof.

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

Z is NH;

- m is 1 and the  $R^1$  group is located at the 5-position and is selected from propoxy,  
 20 isopropoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, pyrrolidin-3-yloxy,  
N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 3-piperidinyloxy, N-methylpiperidin-  
 3-yloxy, 4-piperidinyloxy, N-methylpiperidin-4-yloxy, N-allylpiperidin-4-yloxy,  
N-prop-2-ynylpiperidin-4-yloxy, N-acetylpiperidin-4-yloxy, N-methylsulphonylpiperidin-  
 4-yloxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy,  
 25 N-methylpiperidin-4-ylmethoxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy,

- or m is 2 and the first  $R^1$  group is located at the 5-position and is selected from the  
 group of substituents listed immediately above and the second  $R^1$  group is located at the  
 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy,  
 2-[(3RS,4SR)-3,4-methylenedioxy-pyrrolidin-1-yl]ethoxy,  
 30 3-[(3RS,4SR)-3,4-methylenedioxy-pyrrolidin-1-yl]propoxy, 2-morpholinoethoxy,  
 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy,  
 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy,

3-piperidinopropoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy,  
 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy,  
 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-  
 4-yl)propoxy, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethoxy, 3-(1,2,3,6-tetrahydropyridin-  
 5 1-yl)propoxy, 2-(4-hydroxypiperidin-1-yl)ethoxy, 3-(4-hydroxypiperidin-1-yl)propoxy,  
 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy,  
 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-(4-methylpiperazin-  
 1-yl)butoxy, 2-(4-allylpiperazin-1-yl)ethoxy, 3-(4-allylpiperazin-1-yl)propoxy,  
 2-(4-prop-2-ynylpiperazin-1-yl)ethoxy, 3-(4-prop-2-ynylpiperazin-1-yl)propoxy,  
 10 2-(4-methylsulphonylpiperazin-1-yl)ethoxy, 3-(4-methylsulphonylpiperazin-1-yl)propoxy,  
 2-(4-acetylpiperazin-1-yl)ethoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 4-(4-acetylpiperazin-  
 1-yl)butoxy, 2-(4-isobutyrylpiperazin-1-yl)ethoxy, 3-(4-isobutyrylpiperazin-1-yl)propoxy,  
 4-(4-isobutyrylpiperazin-1-yl)butoxy, 2-[4-(2-fluoroethyl)piperazin-1-yl]ethoxy,  
 3-[4-(2-fluoroethyl)piperazin-1-yl]propoxy, 2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethoxy,  
 15 3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy,  
 3-(4-cyanomethylpiperazin-1-yl)propoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy,  
 2-chloroethoxy, 3-chloropropoxy, 4-chlorobutoxy, 2-methylsulphonylethoxy,  
 3-methylsulphonylpropoxy, 2-(2-methoxyethoxy)ethoxy, 2-(4-pyridyloxy)ethoxy,  
 3-pyridylmethoxy and 2-cyanopyrid-4-ylmethoxy;

20  $R^a$  is chloro or bromo;

$R^b$  is hydrogen, chloro or methoxy; and

$R^d$  is methoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

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

Z is NH;

m is 1 and the  $R^1$  group is located at the 5-position and is selected from propoxy,  
 isopropoxy, tetrahydropyran-4-yloxy, 4-piperidinyloxy and N-methylpiperidin-4-yloxy,

or m is 2 and the first  $R^1$  group is located at the 5-position and is selected from the  
 30 group of substituents listed immediately above, and the second  $R^1$  group is located at the  
 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy,  
 2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy,

3-[(3RS,4SR)-3,4-methylenedioxy-pyrrolidin-1-yl]propoxy, 2-morpholinoethoxy,  
 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy,  
 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy,  
 3-piperidinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-  
 5 1-ylbutoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy,  
 2-(4-allylpiperazin-1-yl)ethoxy, 3-(4-allylpiperazin-1-yl)propoxy, 2-(4-prop-2-ynylpiperazin-  
 1-yl)ethoxy, 3-(4-prop-2-ynylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy,  
 3-(4-acetylpiperazin-1-yl)propoxy, 2-(4-isobutyrylpiperazin-1-yl)ethoxy,  
 3-(4-isobutyrylpiperazin-1-yl)propoxy, 2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethoxy and  
 10 3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy; and

$R^a$  is chloro or bromo;

$R^b$  is hydrogen; and

$R^d$  is methoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

15 A further particular compound of the invention is a quinazoline derivative of the  
 Formula I wherein :

Z is NH;

m is 2 and the first  $R^1$  group is located at the 5-position and is selected from  
 isopropoxy and tetrahydropyran-4-yloxy, and the second  $R^1$  group is located at the 7-position  
 20 and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy,  
 2-[(3RS,4SR)-3,4-methylenedioxy-pyrrolidin-1-yl]ethoxy,  
 3-[(3RS,4SR)-3,4-methylenedioxy-pyrrolidin-1-yl]propoxy, 2-morpholinoethoxy,  
 3-morpholinopropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-(4-methylpiperazin-  
 1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-allylpiperazin-1-yl)ethoxy,  
 25 3-(4-allylpiperazin-1-yl)propoxy, 2-(4-prop-2-ynylpiperazin-1-yl)ethoxy,  
 3-(4-prop-2-ynylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy,  
 3-(4-acetylpiperazin-1-yl)propoxy, 2-(4-isobutyrylpiperazin-1-yl)ethoxy,  
 3-(4-isobutyrylpiperazin-1-yl)propoxy, 2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethoxy and  
 3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy; and

30  $R^a$  is chloro;

$R^b$  is hydrogen; and

$R^d$  is methoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

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

Z is NH;

5        m is 2 and the first R<sup>1</sup> group is located at the 5-position and is selected from isopropoxy and tetrahydropyran-4-yloxy, and the second R<sup>1</sup> group is located at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy and  
10 3-(4-acetylpiperazin-1-yl)propoxy; and

R<sup>a</sup> is chloro;

R<sup>b</sup> is hydrogen; and

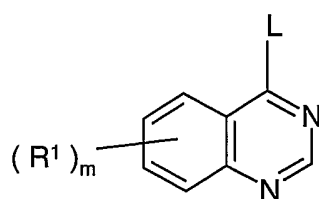
R<sup>d</sup> is methoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

15        A particular compound of the invention is, for example, the quinazoline derivative of the Formula I that is disclosed within Example 2 hereinafter.

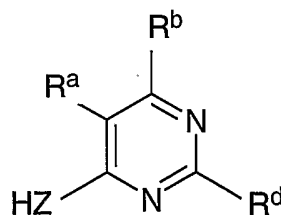
A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a quinazoline derivative  
20 of the Formula I are provided as a further feature of the invention and are illustrated by the following representative process variants in which, unless otherwise stated, Z, m, R<sup>1</sup>, R<sup>a</sup>, R<sup>b</sup> and R<sup>d</sup> have any of the meanings defined hereinbefore. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and  
25 within the accompanying Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

(a) For the production of those compounds of the Formula I wherein Z is an O, S or N(R<sup>2</sup>) group, the reaction of a quinazoline of the Formula II



II

wherein L is a displaceable group and m and R<sup>1</sup> have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a compound of the Formula III



III

- 5 wherein Z is O, S, or N(R<sup>2</sup>) and R<sup>2</sup>, R<sup>a</sup>, R<sup>b</sup> and R<sup>d</sup> 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  
 10 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,  
 15 or, for example, an alkali metal amide, for example sodium hexamethyldisilazane, or, for example, an alkali metal hydride, for example sodium hydride.

A suitable displaceable group L is, for example, a halogeno, alkoxy, aryloxy or sulphonyloxy group, for example a chloro, bromo, methoxy, phenoxy, pentafluorophenoxy, methanesulphonyloxy or toluene-4-sulphonyloxy group. The reaction is conveniently carried  
 20 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, 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 0 to 120°C.

Typically, the quinazoline of the Formula II may be reacted with a compound of the Formula III in the presence of an aprotic solvent such as N,N-dimethylformamide,  
5 conveniently in the presence of a base, for example potassium carbonate or sodium hexamethyldisilazane, and at a temperature in the range, for example, 0 to 150°C, preferably in the range, for example, 0 to 70°C.

The quinazoline derivative of the Formula I may be obtained from this process in the form of the free base or alternatively it may be obtained in the form of a salt with the acid of  
10 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 earth metal carbonate or hydroxide, for example sodium  
15 carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide.

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  
20 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  
25 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  
30 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 acetoxymethyl, 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 (for example trimethylsilylethyl); 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.

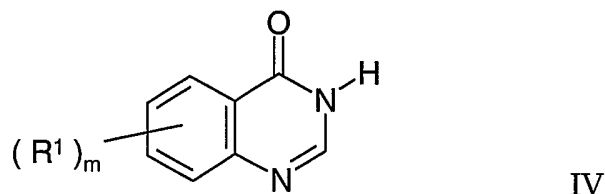
10        Examples of hydroxy protecting groups include lower alkyl groups (for example tert-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxy-carbonyl groups (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl);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

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

25        Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as 2-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as 2-nitrobenzyloxycarbonyl.

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

Quinazoline starting materials of the Formula II may be obtained by conventional procedures such as those disclosed in International Patent Applications WO 01/94341 and WO 02/16352. For example, a 1,4-dihydroquinolin-4-one of Formula IV

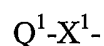


5 wherein m and R<sup>1</sup> have any of the meanings defined hereinbefore except that any functional group is protected if necessary, may be reacted with a halogenating agent such as thionyl chloride, phosphoryl chloride or a mixture of carbon tetrachloride and triphenylphosphine whereafter any protecting group that is present is removed by conventional means.

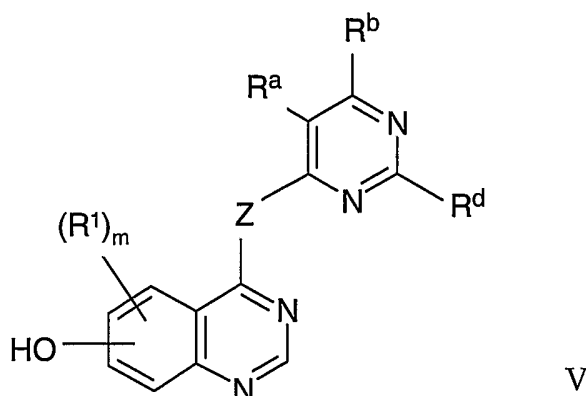
The 4-chloroquinazoline so obtained may be converted, if required, into a  
 10 4-pentafluorophenoxyquinazoline by reaction with pentafluorophenol in the presence of a suitable base such as potassium carbonate and in the presence of a suitable solvent such as N,N-dimethylformamide.

4-Aminopyrimidine starting materials (Formula III, for example when Z is NH) may be obtained by conventional procedures as illustrated in the Examples. Corresponding  
 15 4-hydroxy- and 4-mercaptopyrimidine starting materials (Formula III, when Z is O or S respectively) may be obtained by conventional procedures.

(b) For the production of those compounds of the Formula I wherein at least one R<sup>1</sup> group is a halogeno-(1-6C)alkoxy group or a group of the formula



20 wherein Q<sup>1</sup> is an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group or an optionally substituted alkyl group and X<sup>1</sup> is an oxygen atom, the coupling, conveniently in the presence of a suitable dehydrating agent, of a quinazoline of the Formula V

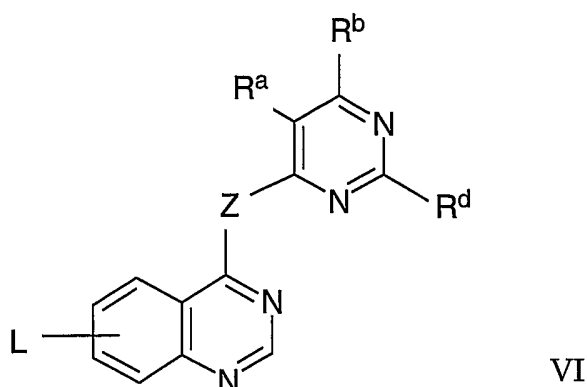


wherein  $m$ ,  $R^1$ ,  $Z$ ,  $R^a$ ,  $R^b$  and  $R^d$  have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an appropriate alcohol wherein any functional group is protected if necessary whereafter any protecting group that is present is  
 5 removed by conventional means.

A suitable dehydrating agent is, for example, a carbodiimide reagent such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or a mixture of an azo compound such as diethyl or di-tert-butyl azodicarboxylate and a phosphine such as triphenylphosphine. The reaction is conveniently carried out in the presence of a suitable inert  
 10 solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride and at a temperature in the range, for example, 10 to 150°C, preferably at or near ambient temperature.

The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon  
 15 tetrachloride and at a temperature in the range, for example, 10 to 150°C, preferably at or near ambient temperature.

(c) For the production of those compounds of the Formula I wherein an  $R^1$  group contains a (1-6C)alkoxy or substituted (1-6C)alkoxy group or a (1-6C)alkylamino or substituted (1-6C)alkylamino group, the reaction, conveniently in the presence of a suitable base as  
 20 defined hereinbefore, of a quinazoline derivative of the Formula VI



wherein L is a displaceable group as defined hereinbefore and Z, R<sup>a</sup>, R<sup>b</sup> and R<sup>d</sup> have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an alcohol or amine as appropriate whereafter any protecting group that is present is removed  
 5 by conventional means.

The reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near 50°C.

(d) For the production of those compounds of the Formula I wherein R<sup>1</sup> is an  
 10 amino-substituted (1-6C)alkoxy group (such as a 2-(4-methylpiperazin-1-yl)ethoxy or 3-dimethylaminopropoxy group), the reaction of a compound of the Formula I wherein R<sup>1</sup> is a halogeno-substituted (1-6C)alkoxy group with a nitrogen-containing heterocyclyl compound or an appropriate amine.

The reaction is conveniently carried out in the presence of a suitable inert diluent or  
 15 carrier as defined hereinbefore and at a temperature in the range 10 to 180°C, preferably in the range 60 to 120°C.

(e) For the production of those compounds of the Formula I wherein R<sup>1</sup> is an amino-hydroxy-disubstituted (1-6C)alkoxy group (such as 2-hydroxy-3-pyrrolidin-1-ylpropoxy or 3-[N-allyl-N-methylamino]-2-hydroxypropoxy), the reaction of a compound of  
 20 the Formula I wherein the R<sup>1</sup> group contains an epoxy-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate amine.

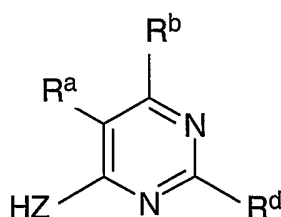
The reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near ambient temperature.

25 (f) For the production of those compounds of the Formula I wherein Z is a SO or SO<sub>2</sub> group, the oxidation of a compound of Formula I wherein Z is a S group.

Conventional oxidation reagents and reaction conditions for such partial or complete oxidation of a sulphur atom are well known to the organic chemist.

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

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 Formula III



III

wherein Z is O, S, or N(R<sup>2</sup>) and R<sup>2</sup>, R<sup>a</sup>, R<sup>b</sup> and R<sup>d</sup> have any of the meanings defined  
10 hereinbefore are novel compounds. For example, although 4-aminopyrimidine starting materials (Formula III, for example when Z is NH) may be obtained by conventional procedures as illustrated in the Examples, compounds such as 4-amino-5-chloro-2-methoxypyrimidine is a novel compound which is provided as a further feature of the invention.

### 15 Biological Assays

The following assays can be used to measure the effects of the compounds of the present invention as c-Src tyrosine kinase inhibitors, as inhibitors *in vitro* of the proliferation of c-Src transfected fibroblast cells, as inhibitors *in vitro* of the migration of A549 human lung tumour cells and as inhibitors *in vivo* of the growth in nude mice of xenografts of A549 tissue.

#### 20 (a) In Vitro Enzyme Assay

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

A substrate solution [100μl of a 20μg/ml solution of the polyamino acid  
25 Poly(Glu, Tyr) 4:1 (Sigma Catalogue No. P0275) in phosphate buffered saline (PBS) containing 0.2mg/ml of sodium azide] was added to each well of a number of Nunc 96-well immunoplates (Catalogue No. 439454) and the plates were sealed and stored at 4°C for 16 hours. The excess of substrate solution was discarded, and aliquots of Bovine Serum

Albumin (BSA; 150µl of a 5% solution in PBS) were transferred into each substrate-coated assay well and incubated for 1 hour at ambient temperature to block non specific binding. The assay plate wells were washed in turn with PBS containing 0.05% v/v Tween 20 (PBST) and with Hepes pH7.4 buffer (50mM, 300µl/well) before being blotted dry.

5 Each test compound was dissolved in dimethyl sulphoxide and diluted with distilled water to give a series of dilutions (from 100µM to 0.001µM). Portions (25µl) of each dilution of test compound were transferred to wells in the washed assay plates. "Total" control wells contained diluted DMSO instead of compound. Aliquots (25µl) of an aqueous magnesium chloride solution (80mM) containing adenosine-5'-triphosphate (ATP; 40µM) was added to all  
10 test wells except the "blank" control wells which contained magnesium chloride without ATP.

Active human c-Src kinase (recombinant enzyme expressed in Sf9 insect cells; obtained from Upstate Biotechnology Inc. product 14-117) was diluted immediately prior to use by a factor of 1:10,000 with an enzyme diluent which comprised 100mM Hepes pH7.4 buffer, 0.2mM sodium orthovanadate, 2mM dithiothreitol and 0.02% BSA. To start the  
15 reactions, aliquots (50µl) of freshly diluted enzyme were added to each well and the plates were incubated at ambient temperature for 20 minutes. The supernatant liquid in each well was discarded and the wells were washed twice with PBST. Mouse IgG anti-phosphotyrosine antibody (Upstate Biotechnology Inc. product 05-321; 100µl) was diluted by a factor of 1:6000 with PBST containing 0.5% w/v BSA and added to each well. The plates were incubated for  
20 1 hour at ambient temperature. The supernatant liquid was discarded and each well was washed with PBST (x4). Horse radish peroxidase (HRP)-linked sheep anti-mouse Ig antibody (Amersham Catalogue No. NXA 931; 100µl) was diluted by a factor of 1:500 with PBST containing 0.5% w/v BSA and added to each well. The plates were incubated for  
1 hour at ambient temperature. The supernatant liquid was discarded and the wells were  
25 washed with PBST (x4).

A PCSB capsule (Sigma Catalogue No. P4922) was dissolved in distilled water (100ml) to provide phosphate-citrate pH5 buffer (50mM) containing 0.03% sodium perborate. An aliquot (50ml) of this buffer was mixed with a 50mg tablet of  
2,2'-azinobis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS; Boehringer Catalogue  
30 No. 1204 521). Aliquots (100µl) of the resultant solution were added to each well. The plates were incubated for 20 to 60 minutes at ambient temperature until the optical density value of the "total" control wells, measured at 405nm using a plate reading spectrophotometer, was

approximately 1.0. "Blank" (no ATP) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity.

(b) In Vitro c-Src transfected NIH 3T3 (c-src 3T3) Fibroblast Proliferation Assay

This assay determined the ability of a test compound to inhibit the proliferation of  
5 National Institute of Health (NIH) mouse 3T3 fibroblast cells that had been stably-transfected with an activating mutant (Y530F) of human c-Src.

Using a similar procedure to that described by Shalloway *et al.*, Cell, 1987, 49, 65-73, NIH 3T3 cells were transfected with an activating mutant (Y530F) of human c-Src. The resultant c-Src 3T3 cells were typically seeded at  $1.5 \times 10^4$  cells per well into 96-well tissue-  
10 culture-treated clear assay plates (Costar) each containing an assay medium comprising Dulbecco's modified Eagle's medium (DMEM; Sigma) plus 0.5% foetal calf serum (FCS), 2mM glutamine, 100 units/ml penicillin and 0.1mg/ml streptomycin in 0.9% aqueous sodium chloride solution. The plates were incubated overnight at 37°C in a humidified (7.5% CO<sub>2</sub> : 95% air) incubator.

15 Test compounds were solubilised in DMSO to form a 10mM stock solution. Aliquots of the stock solution were diluted with the DMEM medium described above and added to appropriate wells. Serial dilutions were made to give a range of test concentrations. Control wells to which test compound was not added were included on each plate. The plates were incubated overnight at 37°C in a humidified (7.5% CO<sub>2</sub> : 95% air) incubator.

20 BrdU labelling reagent (Boehringer Mannheim Catalogue No. 647 229) was diluted by a factor of 1:100 in DMEM medium containing 0.5% FCS and aliquots (20µl) were added to each well to give a final concentration of 10µM. The plates were incubated at 37°C for 2 hours. The medium was decanted. A denaturing solution (FixDenat solution, Boehringer Mannheim Catalogue No. 647 229; 50µl) was added to each well and the plates were placed on  
25 a plate shaker at ambient temperature for 45 minutes. The supernatant was decanted and the wells were washed with PBS (200µl per well). Anti-BrdU-Peroxidase solution (Boehringer Mannheim Catalogue No. 647 229) was diluted by a factor of 1:100 in PBS containing 1% BSA and 0.025% dried skimmed milk (Marvel (registered trade mark), Premier Beverages, Stafford, GB) and an aliquot (100µl) of the resultant solution was added to each well. The  
30 plates were placed on a plate shaker at ambient temperature for 90 minutes. The wells were washed with PBS (x5) to ensure removal of non-bound antibody conjugate. The plates were blotted dry and tetramethylbenzidine substrate solution (Boehringer Mannheim Catalogue

No. 647 229; 100µl) was added to each well. The plates were gently agitated on a plate shaker while the colour developed during a 10 to 20 minute period. The absorbance of the wells was measured at 690nm. The extent of inhibition of cellular proliferation at a range of concentrations of each test compound was determined and an anti-proliferative IC<sub>50</sub> value was  
5 derived.

(c) In Vitro Microdroplet Migration Assay

This assay determines the ability of a test compound to inhibit the migration of adherent mammalian cell lines, for example the human tumour cell line A549.

RPMI medium(Sigma) containing 10% FCS, 1% L-glutamine and 0.3% agarose  
10 (Difco Catalogue No. 0142-01) was warmed to 37°C in a water bath. A stock 2% aqueous agar solution was autoclaved and stored at 42°C. An aliquot (1.5 ml) of the agar solution was added to RPMI medium (10 ml) immediately prior to its use. A549 cells (Accession No. ATCC CCL185) were suspended at a concentration of  $2 \times 10^7$  cells/ml in the medium and maintained at a temperature of 37°C.

15 A droplet (2µl) of the cell/agarose mixture was transferred by pipette into the centre of each well of a number of 96-well, flat bottomed non-tissue-culture-treated microtitre plate (Bibby Sterilin Catalogue No. 642000). The plates were placed briefly on ice to speed the gelling of the agarose-containing droplets. Aliquots (90µl) of medium which had been cooled to 4°C were transferred into each well, taking care not to disturb the microdroplets. Test  
20 compounds were diluted from a 10mM stock solution in DMSO using RPMI medium as described above. Aliquots (10µl) of the diluted test compounds were transferred to the wells, again taking care not to disturb the microdroplets. The plates were incubated at 37°C in a humidified (7.5% CO<sub>2</sub> : 95% air) incubator for about 48 hours.

Migration was assessed visually and the distance of migration was measured back to  
25 the edge of the agar droplet. A migratory inhibitory IC<sub>50</sub> was derived by plotting the mean migration measurement against test compound concentration.

(d) In Vivo A549 Xenograft Growth Assay

This test measures the ability of compounds to inhibit the growth of the A549 human carcinoma grown as a tumour in athymic nude mice (Alderley Park nu/nu strain). A total of  
30 about  $5 \times 10^6$  A549 cells in matrigel (Beckton Dickinson Catalogue No. 40234) were injected subcutaneously into the left flank of each test mouse and the resultant tumours were allowed to grow for about 14 days. Tumour size was measured twice weekly using callipers and a

theoretical volume was calculated. Animals were selected to provide control and treatment groups of approximately equal average tumour volume. Test compounds were 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 was assessed.

5 Although the pharmacological properties of the compounds of the Formula I 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) and (d):-

- Test (a):-  $IC_{50}$  in the range, for example, 0.001 - 10  $\mu M$ ;
- 10 Test (b):-  $IC_{50}$  in the range, for example, 0.1 - 20  $\mu M$ ;
- Test (c):- activity in the range, for example, 0.1-25  $\mu M$ ;
- Test (d):- activity in the range, for example, 1-200 mg/kg/day.

In general, particular compounds of the Formula I such as those provided hereinafter as Examples possess activity at the following concentrations or doses in one or more of the above  
15 tests (a), (b), (c) and (d):-

- Test (a):-  $IC_{50}$  in the range, for example, 0.001 - 0.5  $\mu M$ ;
- Test (b):-  $IC_{50}$  in the range, for example, 0.1 - 5  $\mu M$ ;
- Test (c):- activity in the range, for example, 0.1-5  $\mu M$ ;
- Test (d):- activity in the range, for example, 1-200 mg/kg/day;.

20 For example, the quinazoline compound disclosed within Example 2 possesses the following activity :- Test (a),  $IC_{50}$  approximately 0.015 $\mu M$ ; Test (b),  $IC_{50}$  approximately 0.28 $\mu M$ ; and Test (c) activity at approximately 0.27 $\mu M$ .

No physiologically-unacceptable toxicity was observed in Test (d) at the effective dose for compounds tested of the present invention. Accordingly no untoward toxicological effects  
25 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 quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-  
30 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) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a  
5 suppository for rectal dosing).

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

10 The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent (more suitably from 0.5 to 100 mg, for example from 1 to 30 mg) compounded with an appropriate  
15 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 conditions, the age and sex of the animal or patient and the route of administration, according to well known principles  
20 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, 0.1 mg/kg to 75 mg/kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous  
25 administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.05 mg/kg to 25 mg/kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 0.5 mg to 0.5 g of a compound of this invention.

30 According to a further aspect of the invention there is provided a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

As stated above, it is known that the predominant role of c-Src non-receptor tyrosine kinase is to regulate cell motility which is necessarily required for a localised tumour to progress through the stages of dissemination into the blood stream, invasion of other tissues and initiation of metastatic tumour growth. We have found that the quinazoline derivatives of  
5 the present invention possess potent anti-tumour activity which it is believed is obtained by way of inhibition of one or more of the non-receptor tyrosine-specific protein kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells.

Accordingly the quinazoline derivatives of the present invention are of value as  
10 anti-tumour agents, in particular as selective inhibitors of the motility, dissemination and invasiveness of mammalian cancer cells leading to inhibition of metastatic tumour growth. Particularly, the quinazoline derivatives of the present invention are of value as 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  
15 those tumours which are sensitive to inhibition of one or more of the multiple non-receptor tyrosine kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability 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 the enzyme c-Src, *i.e.* the  
20 compounds may be used to produce a c-Src enzyme inhibitory effect in a warm-blooded animal in need of such treatment. Specifically, the compounds of the present invention are expected to be useful in the prevention or treatment of solid tumour disease.

Thus according to this aspect of the invention there is provided a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore for use  
25 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 the use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

30 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 quinazoline 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 quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, as defined

5 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  
10 amount of a quinazoline 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 quinazoline 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  
15 those tumours which are sensitive to inhibition of non-receptor tyrosine kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising 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 non-  
20 receptor tyrosine kinases such as c-Src kinase that are involved in the signal transduction steps which lead to the invasiveness and migratory ability of metastasising tumour cells which comprises administering to said animal an effective amount of a quinazoline 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 quinazoline  
25 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 c-Src kinase inhibitory effect.

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

- (i) other anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

- (ii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside and hydroxyurea; antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);
- (iii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and idoxifene), 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 $\alpha$ -reductase such as finasteride;
- (iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [Herceptin™] and the anti-erbB1 antibody cetuximab [C225]), farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;
- (v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds

that work by other mechanisms (for example linomide, inhibitors of integrin  $\alpha v\beta 3$  function and angiostatin);

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

5 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  
10 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  
15 as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

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

According to this aspect of the invention there is provided a pharmaceutical product comprising a quinazoline derivative of the formula I as defined hereinbefore and an additional  
25 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 for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of c-Src. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

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

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

(ii) evaporations were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids by filtration;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck  
5 Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany or high pressure liquid chromatography (HPLC) was performed on C18 reverse phase silica, for example on a Waters C-18 5 microns preparative reversed-phase column;

(iv) yields, where present, are not necessarily the maximum attainable;

(v) in general, the end-products of the Formula I have satisfactory microanalyses and  
10 their structures were confirmed by nuclear magnetic resonance (NMR) and/or mass spectral techniques; fast-atom bombardment (FAB) mass spectral data were obtained using a Platform spectrometer and, where appropriate, either positive ion data or negative ion data were collected; NMR chemical shift values were measured on the delta scale [proton magnetic resonance spectra were determined using a Jeol JNM EX 400 spectrometer operating at a field  
15 strength of 400MHz, Varian Gemini 2000 spectrometer operating at a field strength of 300MHz or a Bruker AM300 spectrometer operating at a field strength of 300MHz]; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad;

(vi) intermediates were not generally fully characterised and purity was assessed by  
20 thin layer chromatographic, HPLC, infra-red (IR) and/or NMR analysis;

(vii) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus; melting points for the end-products of the Formula I were determined after crystallisation from a conventional organic solvent such as ethanol, methanol, acetone, ether or hexane, alone or in admixture;

25 (viii) where certain compounds were obtained as an acid-addition salt, for example a mono hydrochloride salt or a dihydrochloride 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;

(ix) the following abbreviations have been used:-

|    |      |                               |
|----|------|-------------------------------|
| 30 | DMF  | <u>N,N</u> -dimethylformamide |
|    | DMSO | dimethylsulphoxide            |
|    | THF  | tetrahydrofuran               |
|    | DMA  | <u>N,N</u> -dimethylacetamide |

**Example 1****7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2-methoxypyrimidin-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline**

Sodium hexamethyldisilazane (1M solution in THF; 1.38 ml) was added dropwise to a mixture of 4-amino-5-chloro-2-methoxypyrimidine (0.11 g), 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-chloro-5-tetrahydropyran-4-yloxyquinazoline (0.3 g) and THF (4 ml) that had been cooled to 0°C and the mixture was stirred at 0°C for 5 minutes and at ambient temperature for 18 hours. Glacial acetic acid (0.083 ml) was added followed by methanol (10 ml). The reaction mixture was evaporated and the residue was dissolved in a 7M methanolic ammonia solution. The resultant mixture was evaporated and the residue was diluted with methylene chloride and the solids were filtered off. The filtrate was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. The material so obtained was triturated under diethyl ether. There was thus obtained the title compound as a solid (0.078 g);

NMR Spectrum: (DMSO-d<sub>6</sub>) 1.7 (m, 2H), 2.0 (s, 3H), 2.06 (m, 2H), 2.45 (m, 2H), 2.78 (m, 2H), 3.5-3.3 (m, 8H), 3.83 (s, 3H), 3.85 (m, 2H), 4.28 (m, 2H), 4.98 (m, 1H), 6.95 (m, 2H), 8.58 (s, 1H), 8.67 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 558 and 560.

The 4-amino-5-chloro-2-methoxypyrimidine used as a starting material were prepared as follows :-

A 6M methanolic ammonia solution (20 ml) was added to 2,4,5-trichloropyrimidine (J. Chesterfield *et al.*, J. Chem. Soc., 1955, 3478; 2 g) and the resultant mixture was stirred at ambient temperature for 24 hours. The mixture was evaporated. Water was added and the pH of the solution was adjusted to 8.5. The resultant white solid was isolated, washed with water and dried under vacuum. The material so obtained was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained 4-amino-2,5-dichloropyrimidine as a white solid (1.34 g); Mass Spectrum: M+H<sup>+</sup> 164.

A portion (1.1 g) of the material so obtained was added portionwise to a solution of sodium methoxide (1.27 g) in methanol (35 ml). The resultant mixture was heated to 60°C for 45 minutes. The mixture was cooled to ambient temperature and evaporated. The residue was partitioned between methylene chloride and water. The pH of the aqueous layer was adjusted to 8 and the organic extract was separated, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 100:3 mixture of

methylene chloride and methanol as eluent. There was thus obtained 4-amino-5-chloro-2-methoxypyrimidine as a white solid (1.04 g); NMR Spectrum: (CDCl<sub>3</sub>) 3.91 (s, 3H), 5.41 (m, 2H), 8.04 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 160.

The 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-chloro-5-tetrahydropyran-

5 4-yloxyquinazoline used as a starting material were prepared as follows :-

Sodium hydride (60% dispersion in mineral oil; 0.6 g) was added portionwise to a solution of 4-hydroxytetrahydropyran (0.78 g) in DMF (10 ml) that had been cooled to 5°C.

The mixture was allowed to warm to ambient temperature and was stirred for 15 minutes.

5,7-Difluoro-3,4-dihydroquinazolin-4-one (International Patent Application WO 01/94341;

10 0.9 g) was added and the mixture was stirred at ambient temperature for 30 minutes. The mixture was poured into water (100 ml) and, with vigorous stirring, glacial acetic acid was added to acidify the mixture to pH5. The resultant solid was isolated, washed with water and with diethyl ether and dried under vacuum. There was thus obtained 7-fluoro-5-tetrahydropyran-4-yloxy-3,4-dihydroquinazolin-4-one (1.1 g); NMR Spectrum: (DMSO-d<sub>6</sub>)  
15 1.6-1.75 (m, 2H), 1.9-2.0 (m, 2H), 3.5-3.6 (m, 2H), 3.85-3.95 (m, 2H), 4.8 (m, 1H), 6.9 (m, 1H), 7.05 (m, 1H), 8.0 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 265.

After repetition of the prior reaction, a mixture of 7-fluoro-5-tetrahydropyran-

4-yloxy-3,4-dihydroquinazolin-4-one (5.3 g), 2-piperazin-1-ylethanol (3.9 g), potassium

tert-butoxide (6.7 g) and THF (200 ml) was stirred and heated to reflux for 3 hours. A second

20 portion (6.7 g) of potassium tert-butoxide was added and the mixture was heated to reflux for a further 12 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a 7M methanolic ammonia solution as eluent. The material so obtained was triturated under diethyl ether. There was thus obtained  
25 7-(2-piperazin-1-ylethoxy)-5-tetrahydropyran-4-yloxy-3,4-dihydroquinazolin-4-one (5.2 g); NMR Spectrum: (DMSO-d<sub>6</sub> and CF<sub>3</sub>CO<sub>2</sub>D) 1.75 (m, 2H), 2.03 (m, 2H), 3.2-4.0 (m, 14H), 4.59 (m, 2H), 4.92 (m, 1H), 6.88 (s, 1H), 6.9 (s, 1H), 9.28 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 375.

Acetic anhydride (1.51 ml) was added dropwise to a stirred mixture of

7-(2-piperazin-1-ylethoxy)-5-tetrahydropyran-4-yloxy-3,4-dihydroquinazolin-4-one (5 g) and

30 water (20 ml) and the resultant mixture was stirred at ambient temperature for 10 minutes.

The reaction mixture was evaporated and the residue was triturated under diethyl ether. The resultant solid was isolated, washed with diethyl ether and dried under vacuum. There was thus obtained 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxy-

3,4-dihydroquinazolin-4-one (5.5 g); NMR Spectrum: (DMSO<sub>d</sub><sub>6</sub> and CF<sub>3</sub>CO<sub>2</sub>D) 1.75 (m, 2H), 2.03 (m, 2H), 2.08 (s, 3H), 3.0-4.2 (m, 13H), 4.56 (m, 3H), 4.94 (m, 1H), 6.84 (s, 1H), 6.9 (s, 1H), 9.21 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 417.

A mixture of a portion (0.416 g) of the material so obtained, triphenylphosphine (0.655 g), carbon tetrachloride (0.34 ml) and 1,2-dichloroethane (20 ml) was stirred and heated to 70°C for 1.5 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a 7M methanolic ammonia solution (a solvent gradient having from 1% to 3% methanolic ammonia solution) as eluent. There was thus obtained 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-chloro-5-tetrahydropyran-4-yloxyquinazoline as a solid (0.35 g); NMR Spectrum: (CDCl<sub>3</sub>) 2.0 (m, 2H), 2.1 (s, 3H), 2.12 (m, 2H), 2.58 (m, 4H), 2.9 (m, 2H), 3.51 (m, 2H), 3.68 (m, 4H), 4.05 (m, 2H), 4.25 (m, 2H), 4.75 (m, 1H), 6.62 (s, 1H), 6.94 (s, 1H), 8.82 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 435 and 437.

## 15 Example 2

### **7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2-methoxypyrimidin-4-ylamino)-5-isopropoxyquinazoline**

Using an analogous procedure to that described in Example 1 except that the sodium hexamethyldisilazane solution was added dropwise to a mixture of 4-amino-5-chloro-2-methoxypyrimidine, 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-chloro-5-isopropoxyquinazoline and THF that had been cooled to -40°C and the resultant mixture was stirred and allowed to warm to ambient temperature and stirred at ambient temperature for 2 hours. After an analogous work-up to that described in Example 1, the title compound was obtained as a solid in 14% yield; NMR Spectrum: (DMSO<sub>d</sub><sub>6</sub>) 1.37 (s, 3H), 1.38 (s, 3H), 1.99 (s, 3H), 2.46 (m, 2H), 2.79 (m, 2H), 3.4-3.3 (m, 6H), 3.83 (s, 3H), 4.28 (m, 2H), 5.0 (m, 1H), 6.82 (s, 1H), 6.94 (s, 1H), 8.58 (s, 1H), 8.68 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 516 and 518.

The 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-chloro-5-isopropoxyquinazoline that was used as a starting material was prepared using analogous procedures to those described in the portion of Example 1 that is concerned with the preparation of starting materials. Thus :-

5,7-Difluoro-3,4-dihydroquinazolin-4-one was reacted with isopropanol to give 7-fluoro-5-isopropoxy-3,4-dihydroquinazolin-4-one in 73% yield; NMR Spectrum: (DMSO<sub>d</sub><sub>6</sub>) 1.31 (s, 6H), 4.73 (m, 1H), 6.89 (m, 1H), 6.95 (m, 1H), 7.96 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 223.

The material so obtained was reacted with 2-piperazin-1-ylethanol to give 5-isopropoxy-7-(2-piperazin-1-ylethoxy)-3,4-dihydroquinazolin-4-one in 63% yield; NMR Spectrum: (CDCl<sub>3</sub>) 1.45 (s, 3H), 1.46 (s, 3H), 2.4-3.0 (m, 10H), 4.2 (t, 2H), 4.62 (m, 1H), 6.51 (s, 1H), 6.72 (s, 1H), 7.9 (s, 1H).

5 The material so obtained was reacted with an excess of acetic anhydride but using methylene chloride rather than water as the reaction solvent. The reaction mixture was stirred at ambient temperature for 15 minutes. The mixture was partitioned between methylene chloride and a saturated aqueous sodium bicarbonate solution. The organic layer was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was  
10 triturated under a mixture of acetonitrile and diethyl ether. There was thus obtained 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-5-isopropoxy-3,4-dihydroquinazolin-4-one in 70% yield; NMR Spectrum: (CDCl<sub>3</sub>) 1.46 (s, 3H), 1.47 (s, 3H), 2.1 (s, 3H), 2.58 (m, 4H), 2.87 (t, 2H), 3.5 (m, 2H), 3.66 (m, 2H), 4.21 (t, 2H), 4.63 (m, 1H), 6.51 (s, 1H), 6.72 (s, 1H), 7.9 (s, 1H), 9.9 (br s, 1H); Mass Spectrum: M+H<sup>+</sup> 375.

15 The material so obtained was reacted with carbon tetrachloride and triphenylphosphine to give 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-chloro-5-isopropoxyquinazoline in 68% yield which was used without further purification; Mass Spectrum: M+H<sup>+</sup> 393.

### Example 3

#### 20 **4-(5-chloro-2-methoxypyrimidin-4-ylamino)-7-(2,4-dimethoxybenzyloxy)-5-isopropoxyquinazoline**

Sodium hexamethyldisilazane (1M solution in THF; 8.2 ml) was added dropwise to a mixture of 4-amino-5-chloro-2-methoxypyrimidine (0.65 g), 4-chloro-7-(2,4-dimethoxybenzyloxy)-5-isopropoxyquinazoline (1.65 g) and THF (20 ml) that had been  
25 cooled to -30°C and the mixture was stirred at -30°C for 5 minutes and at ambient temperature for 2 hours. DMF (15 ml) was added and the mixture was stirred at ambient temperature for a further 5 hours. Glacial acetic acid (0.49 ml) was added and the solvents were evaporated. A 7M methanolic ammonia solution was added and the mixture was again evaporated. The residue was purified by column chromatography on silica using a 30:1 mixture of methylene  
30 chloride and methanol as eluent. There was thus obtained the title compound as a solid (1.46 g); NMR Spectrum: (CDCl<sub>3</sub>) 1.53 (s, 3H), 1.54 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 4.01

(s, 3H), 4.84 (m, 1H), 5.16 (s, 2H), 6.52 (m, 2H), 6.66 (s, 1H), 7.05 (s, 1H), 7.34 (d, 1H), 8.36 (s, 1H), 8.83 (s, 1H); Mass Spectrum:  $M+H^+$  512 and 514.

The 4-chloro-7-(2,4-dimethoxybenzyloxy)-5-isopropoxyquinazoline used as a starting material were prepared as follows :-

- 5 A mixture of 7-fluoro-5-isopropoxy-3,4-dihydroquinazolin-4-one (61 g), 2,4-dimethoxybenzyl alcohol (138 g), potassium *tert*-butoxide (185 g) and THF (1.5 litres) was stirred and heated to reflux for 18 hours. After cooling, the solvent was evaporated and a mixture of methylene chloride (400 ml) and water (600 ml) was added. With cooling, the 2-phase mixture was neutralised by the addition of 2N aqueous hydrochloric acid. The
- 10 mixture was filtered and the organic phase was separated, dried over magnesium sulphate and evaporated. The residue was triturated under diethyl ether. There was thus obtained 7-(2,4-dimethoxybenzyloxy)-5-isopropoxy-3,4-dihydroquinazolin-4-one (68 g); NMR Spectrum: (DMSO<sub>d</sub><sub>6</sub>) 1.28 (s, 6H), 3.78 (s, 3H), 3.82 (s, 3H), 4.63 (m, 1H), 5.06 (s, 2H), 6.55 (m, 2H), 6.62 (s, 1H), 6.71 (s, 1H), 7.33 (d, 1H), 7.88 (s, 1H); Mass Spectrum:  $M+H^+$  371.
- 15 A mixture of a portion (4 g) of the material so obtained, phosphorus oxychloride (1.98 g), diisopropylethylamine (3.6 g) and methylene chloride (100 ml) was stirred and heated to 75°C for 3 hours. The mixture was cooled and evaporated. The residue was dried under vacuum for 1 hour and purified by column chromatography on silica using a 20:3 mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained 4-chloro-
- 20 7-(2,4-dimethoxybenzyloxy)-5 isopropoxyquinazoline as a solid (2.63 g); NMR Spectrum: (CDCl<sub>3</sub>) 1.46 (s, 3H), 1.47 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 4.68 (m, 1H), 5.16 (s, 2H), 6.52 (m, 2H), 6.65 (s, 1H), 7.06 (s, 1H), 7.33 (d, 1H), 8.78 (s, 1H); Mass Spectrum:  $M+H^+$  389.

#### Example 4

#### 25 **4-(5-chloro-2-methoxypyrimidin-4-ylamino)-7-hydroxy-5-isopropoxyquinazoline**

- Trifluoroacetic acid (5 ml) was added to a solution of 4-(5-chloro-2-methoxypyrimidin-4-ylamino)-7-(2,4-dimethoxybenzyloxy)-5-isopropoxyquinazoline (1.65 g) in methylene chloride (20 ml) and the reaction mixture was stirred at ambient temperature for 1 hour. The solvents were evaporated. The residue was triturated under
- 30 diethyl ether. There was thus obtained the title compound as a trifluoroacetic acid salt in quantitative yield; Mass Spectrum:  $M+H^+$  362 and 364.

**Example 5****7-(2-chloroethoxy)-4-(5-chloro-2-methoxypyrimidin-4-ylamino)-5-isopropoxyquinazoline**

A mixture of 4-(5-chloro-2-methoxypyrimidin-4-ylamino)-7-hydroxy-5-isopropoxyquinazoline trifluoroacetic acid salt (0.85 g), 1,2-dichloroethane (10 ml), potassium carbonate (1 g) and DMF (5 ml) was stirred and heated to 80°C for 2 hours. After cooling, the solids were filtered off and the filtrate was evaporated. The residue was purified by column chromatography on silica using a 100:1 mixture of methylene chloride and methanol as eluent. There was thus obtained the title compound (0.41 g); Mass Spectrum:  $M+H^+$  424 and 426.

10

**Example 6****7-(3-chloropropoxy)-4-(5-chloro-2-methoxypyrimidin-4-ylamino)-5-isopropoxyquinazoline**

A mixture of 4-(5-chloro-2-methoxypyrimidin-4-ylamino)-7-hydroxy-5-isopropoxyquinazoline trifluoroacetic acid salt (0.85 g), 1-bromo-3-chloropropane (0.16 ml), caesium carbonate (0.73 g) and DMF (8 ml) was stirred and heated to 60°C for 45 minutes. After cooling, the solids were filtered off and the filtrate was evaporated. The residue was purified by column chromatography on silica using a 50:1 mixture of methylene chloride and methanol as eluent. There was thus obtained the title compound (0.238 g); NMR Spectrum: ( $CDCl_3$ ) 1.56 (s, 3H), 1.57 (s, 3H), 2.32 (m, 2H), 3.76 (t, 2H), 4.02 (s, 3H), 4.27 (t, 2H), 4.87 (m, 1H), 6.6 (s, 1H), 6.92 (s, 1H), 8.37 (s, 1H), 8.84 (s, 1H); Mass Spectrum:  $M+H^+$  438 and 440.

20

**Example 7****4-(5-chloro-2-methoxypyrimidin-4-ylamino)-5-isopropoxy-7-(2-morpholinoethoxy)quinazoline**

A mixture of 7-(2-chloroethoxy)-4-(5-chloro-2-methoxypyrimidin-4-ylamino)-5-isopropoxyquinazoline (0.085 g; 0.2 mmol), morpholine (0.07 g; 0.8 mmol), potassium iodide (0.132 g; 0.4 mmol) and DMA (1 ml) was stirred and heated to 90°C for 2.5 hours. The reaction mixture was cooled to ambient temperature and filtered and the filtrate was injected directly on to a Waters X-Terra column (C18 reversed-phase, 5 microns, 20 mm diameter,

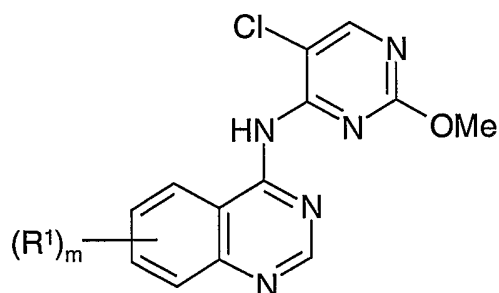
30

100 mm length) and eluted with decreasingly polar mixtures of 0.032M aqueous ammonium formate solution and acetonitrile. The material so obtained was triturated under diethyl ether. There was thus obtained the title compound as a solid (0.007 g); NMR Spectrum: (CDCl<sub>3</sub>) 1.56 (s, 3H), 1.57 (s, 3H), 2.88 (m, 4H), 3.11 (m, 2H), 3.95 (m, 4H), 4.02 (s, 3H), 4.41 (m, 2H), 4.91 (m, 1H), 6.77 (br s, 1H), 6.93 (s, 1H), 8.38 (s, 1H), 8.83 (s, 1H); Mass Spectrum: M+H<sup>+</sup> 475 and 477.

### Example 8

Using analogous procedures and quantities of reactants to those described in Example 7, the appropriate 7-haloalkoxyquinazoline was reacted with the appropriate heterocyclic compound to give the compounds described in Table I. Unless otherwise stated, each compound described in Table I was obtained as a free base.

Table I



15

| Compound No. & Note | (R <sup>1</sup> ) <sub>m</sub>                     |
|---------------------|----------------------------------------------------|
| [1]                 | 5-isopropoxy-7-[2-(4-methylpiperazin-1-yl)ethoxy]  |
| [2]                 | 5-isopropoxy-7-(2-pyrrolidin-1-ylethoxy)           |
| [3]                 | 5-isopropoxy-7-(3-morpholinopropoxy)               |
| [4]                 | 5-isopropoxy-7-[3-(4-methylpiperazin-1-yl)propoxy] |
| [5]                 | 5-isopropoxy-7-[3-(4-acetylpiperazin-1-yl)propoxy] |
| [6]                 | 5-isopropoxy-7-(3-pyrrolidin-1-ylpropoxy)          |

### Notes

[1] The reaction yielded 0.042 g of the required product which gave the following characterising data; NMR Spectrum: (CDCl<sub>3</sub>) 1.55 (s, 3H), 1.56 (s, 3H), 2.31 (s, 3H), 2.5

(m, 4H), 2.64 (m, 4H), 2.88 (m, 2H), 4.01 (s, 3H), 4.25 (m, 2H), 4.87 (m, 1H), 6.64 (s, 1H), 6.9 (s, 1H), 8.37 (s, 1H), 8.83 (s, 1H); Mass Spectrum:  $M+H^+$  488 and 490.

[2] The reaction yielded 0.01 g of the required product which gave the following characterising data; NMR Spectrum: ( $CDCl_3$ ) 1.54 (s, 3H), 1.55 (s, 3H), 1.83 (m, 4H), 2.64 (m, 4H), 2.97 (m, 2H), 4.01 (s, 3H), 4.24 (m, 2H), 4.85 (m, 1H), 6.67 (s, 1H), 6.9 (s, 1H), 8.36 (s, 1H), 8.83 (s, 1H); Mass Spectrum:  $M+H^+$  459 and 461.

[3] The reaction yielded 0.031 g of the required product which gave the following characterising data; NMR Spectrum: ( $CDCl_3$ ) 1.54 (s, 3H), 1.55 (s, 3H), 2.04 (m, 2H), 2.49 (m, 4H), 2.55 (m, 2H), 3.73 (m, 4H), 4.01 (s, 3H), 4.18 (m, 2H), 4.87 (m, 1H), 6.59 (s, 1H), 6.91 (s, 1H), 8.37 (s, 1H), 8.83 (s, 1H); Mass Spectrum:  $M+H^+$  489 and 491.

[4] The reaction yielded 0.011 g of the required product which gave the following characterising data; NMR Spectrum: ( $CDCl_3$ ) 1.55 (s, 3H), 1.56 (s, 3H), 2.04 (m, 2H), 2.3 (s, 3H), 2.5 (m, 8H), 2.56 (m, 2H), 4.01 (s, 3H), 4.16 (m, 2H), 4.87 (m, 1H), 6.59 (s, 1H), 6.9 (s, 1H), 8.36 (s, 1H), 8.82 (s, 1H); Mass Spectrum:  $M+H^+$  502 and 504.

[5] The reaction yielded 0.03 g of the required product which gave the following characterising data; NMR Spectrum: ( $CDCl_3$ ) 1.55 (s, 3H), 1.56 (s, 3H), 2.04 (m, 2H), 2.1 (s, 3H), 2.47 (m, 4H), 2.57 (m, 2H), 3.48 (m, 2H), 3.64 (m, 2H), 4.01 (s, 3H), 4.18 (m, 2H), 4.87 (m, 1H), 6.59 (s, 1H), 6.91 (s, 1H), 8.37 (s, 1H), 8.83 (s, 1H); Mass Spectrum:  $M+H^+$  530 and 532.

[6] The reaction yielded 0.014 g of the required product which gave the following characterising data; Mass Spectrum:  $M+H^+$  473 and 475.

### **Example 9**

#### **4-(5-chloro-2-methoxypyrimidin-4-ylamino)-6-methoxy-**

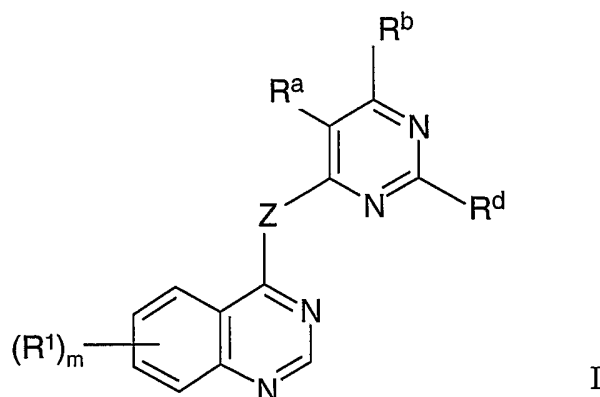
#### **7-(3-morpholinopropoxy)quinazoline**

Using an analogous procedure to that described in Example 1 except that the sodium hexamethyldisilazane solution (1M solution in THF; 1.78 ml) was added dropwise to a mixture of 4-amino-5-chloro-2-methoxypyrimidine (0.142 g), 4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (International Patent Application WO 02/16352, example 1 thereof; 0.3 g) and THF (6 ml) that had been cooled to  $-20^\circ C$  and the resultant mixture was stirred and allowed to warm to ambient temperature and stirred at ambient temperature for 48 hours. After an analogous work-up to that described in Example 1, the title compound was obtained as a solid in 19% yield; NMR Spectrum: ( $CDCl_3$ ) 2.12 (m, 2H), 2.48

(m, 4H), 2.56 (t, 2H), 3.73 (m, 4H), 4.01 (s, 3H), 4.05 (s, 3H), 4.26 (t, 2H), 7.19 (s, 1H), 8.06 (br s, 1H), 8.18 (br s, 1H), 8.33 (s, 1H); Mass Spectrum:  $M+H^+$  461 and 463.

**CLAIMS**

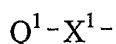
1. A quinazoline derivative of the Formula I



- 5 wherein **Z** is an O, S, SO, SO<sub>2</sub>, N(R<sup>2</sup>) or C(R<sup>2</sup>)(R<sup>3</sup>) group wherein each R<sup>2</sup> or R<sup>3</sup> group, which may be the same or different, is hydrogen or (1-8C)alkyl;

**m** is 1, 2 or 3;

- each R<sup>1</sup> group**, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, (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, 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)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 :

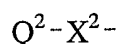


- wherein X<sup>1</sup> is a direct bond or is selected from O, S, SO, SO<sub>2</sub>, N(R<sup>4</sup>), CO, CH(OR<sup>4</sup>), CON(R<sup>4</sup>), N(R<sup>4</sup>)CO, SO<sub>2</sub>N(R<sup>4</sup>), N(R<sup>4</sup>)SO<sub>2</sub>, OC(R<sup>4</sup>)<sub>2</sub>, SC(R<sup>4</sup>)<sub>2</sub> and N(R<sup>4</sup>)C(R<sup>4</sup>)<sub>2</sub>, wherein R<sup>4</sup> is hydrogen or (1-8C)alkyl, and Q<sup>1</sup> 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, or (R<sup>1</sup>)<sub>m</sub> is (1-3C)alkylenedioxy,

- and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R<sup>1</sup> substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO<sub>2</sub>, N(R<sup>5</sup>), CO, CH(OR<sup>5</sup>), CON(R<sup>5</sup>), N(R<sup>5</sup>)CO, SO<sub>2</sub>N(R<sup>5</sup>), N(R<sup>5</sup>)SO<sub>2</sub>, CH=CH and C≡C wherein

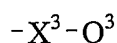
$R^5$  is hydrogen or (1-8C)alkyl or, when the inserted group is  $N(R^5)$ ,  $R^5$  may also be (2-6C)alkanoyl,

and wherein any  $CH_2=CH-$  or  $HC\equiv C-$  group within a  $R^1$  substituent optionally bears at the terminal  $CH_2=$  or  $HC\equiv$  position a substituent selected from halogeno, carboxy, carbamoyl, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :



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

and wherein any  $CH_2$  or  $CH_3$  group within a  $R^1$  substituent optionally bears on each said  $CH_2$  or  $CH_3$  group one or more halogeno or (1-8C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, oxo, thioxo, (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)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 :

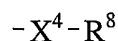


wherein  $X^3$  is a direct bond or is selected from O, S, SO,  $SO_2$ ,  $N(R^7)$ , CO,  $CH(OR^7)$ ,  $CON(R^7)$ ,  $N(R^7)CO$ ,  $SO_2N(R^7)$ ,  $N(R^7)SO_2$ ,  $C(R^7)_2O$ ,  $C(R^7)_2S$  and  $N(R^7)C(R^7)_2$ , wherein  $R^7$  is hydrogen or (1-8C)alkyl, and  $Q^3$  is aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (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, heteroaryl or heterocyclyl group within a  $R^1$  substituent optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (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,

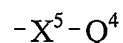
di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl,  
N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino,  
N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl,  
N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, N-(1-6C)alkyl-

5 (1-6C)alkanesulphonylamino and (1-3C)alkylenedioxy, or from a group of the formula :



wherein  $X^4$  is a direct bond or is selected from O and N( $R^9$ ), wherein  $R^9$  is hydrogen or  
 (1-8C)alkyl, and  $R^8$  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-

10 (1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl,  
 or from a group of the formula :



wherein  $X^5$  is a direct bond or is selected from O, N( $R^{10}$ ) and CO, wherein  $R^{10}$  is hydrogen or  
 (1-8C)alkyl, and  $Q^4$  is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or  
 15 heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or  
 different, selected from halogeno, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and  
 (1-6C)alkoxy,

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

20  $R^a$  is hydrogen or halogeno;

$R^b$  is hydrogen, halogeno, (1-8C)alkyl or (1-6C)alkoxy; and

$R^d$  is (1-6C)alkoxy; and

or a pharmaceutically-acceptable salt thereof.

25 2. A quinazoline derivative of the Formula I according to claim 1 wherein each of Z, m,  
 $R^1$  and  $R^b$  has any of the meanings defined in claim 1 and  $R^a$  is halogeno and  $R^d$  is methoxy.

3. A quinazoline derivative of the Formula I according to claim 1 wherein :-  
 Z is NH;

30 m is 2 and the  $R^1$  groups, which may be the same or different, are located at the 6- and  
 7-positions and the  $R^1$  group at the 6-position is selected from hydroxy, methoxy, ethoxy and  
 propoxy, and the  $R^1$  group at the 7-position is selected from methoxy, ethoxy, propoxy,

2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy,  
 pyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 2-pyrrolidin-2-ylethoxy,  
 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 4-morpholinobutoxy,  
 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-  
 5 4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy,  
 piperidin-3-yloxy, piperidin-4-yloxy, piperidin-3-ylmethoxy, 2-piperidin-3-ylethoxy,  
 piperidin-4-ylmethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy,  
 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy,  
 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and  
 10 3-homopiperazin-1-ylpropoxy,

and wherein any CH<sub>2</sub> or CH<sub>3</sub> group within a R<sup>1</sup> substituent optionally bears on each  
 said CH<sub>2</sub> or CH<sub>3</sub> group one or more chloro groups or a substituent selected from hydroxy, oxo,  
 amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino,  
N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxy,

15 and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2  
 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl,  
 hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidendioxy and  
 isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl,  
 piperazin-1-yl or homopiperazin-1-yl group within a R<sup>1</sup> substituent is optionally N-substituted  
 20 with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl,  
 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2  
 oxo substituents;

R<sup>a</sup> is hydrogen, chloro or bromo;

25 R<sup>b</sup> is hydrogen, fluoro, chloro, bromo, methoxy or ethoxy; and

R<sup>d</sup> is methoxy or ethoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

4. A quinazoline derivative of the Formula I according to claim 1 wherein :-

30 Z is NH;

m is 2 and the first R<sup>1</sup> group is a 6-methoxy group and the second R<sup>1</sup> group is located at  
 the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy,

2-[(3RS,4SR)-3,4-methylenedioxy-pyrrolidin-1-yl]ethoxy,  
 3-[(3RS,4SR)-3,4-methylenedioxy-pyrrolidin-1-yl]propoxy, 2-morpholinoethoxy,  
 3-morpholinopropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-(4-methylpiperazin-  
 1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-allylpiperazin-1-yl)ethoxy,  
 5 3-(4-allylpiperazin-1-yl)propoxy, 2-(4-prop-2-ynylpiperazin-1-yl)ethoxy,  
 3-(4-prop-2-ynylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy,  
 3-(4-acetylpiperazin-1-yl)propoxy, 2-(4-isobutyrylpiperazin-1-yl)ethoxy,  
 3-(4-isobutyrylpiperazin-1-yl)propoxy, 2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethoxy and  
 3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy; and

- 10         $R^a$  is chloro;  
            $R^b$  is hydrogen; and  
            $R^d$  is methoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

15 5. A quinazoline derivative of the Formula I according to claim 1 wherein :-

Z is NH;

- m is 2 and the  $R^1$  groups, which may be the same or different, are located at the 5- and  
 7-positions and the  $R^1$  group at the 5-position is selected from methoxy, ethoxy, propoxy,  
 isopropoxy, butoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, pyrrolidin-3-yloxy,  
 20 pyrrolidin-2-ylmethoxy, 3-piperidinyloxy, 4-piperidinyloxy, piperidin-3-ylmethoxy,  
 piperidin-4-ylmethoxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy, and the  $R^1$  group at  
 the 7-position is selected from hydroxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy,  
 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 4-pyrrolidin-1-ylbutoxy,  
 2-pyrrolidin-2-ylethoxy, 3-pyrrolidin-2-ylpropoxy, 2-morpholinoethoxy,  
 25 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-  
 4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy,  
 3-piperidinopropoxy, 4-piperidinobutoxy, 2-piperidin-3-ylethoxy, 2-piperidin-4-ylethoxy,  
 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-  
 1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy  
 30 and 3-homopiperazin-1-ylpropoxy,

and wherein any  $CH_2$  or  $CH_3$  group within a  $R^1$  substituent optionally bears on each  
 said  $CH_2$  or  $CH_3$  group one or more chloro groups or a substituent selected from hydroxy, oxo,

amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxy,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidendioxy and isopropylidendioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R<sup>1</sup> substituent is optionally N-substituted with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

and wherein any heterocyclyl group within a substituent on R<sup>1</sup> optionally bears 1 or 2 oxo substituents;

R<sup>a</sup> is hydrogen, chloro or bromo;

R<sup>b</sup> is hydrogen, fluoro, chloro, bromo, methoxy or ethoxy; and

R<sup>d</sup> is methoxy or ethoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

6. A quinazoline derivative of the Formula I according to claim 1 wherein :-

Z is NH;

m is 1 and the R<sup>1</sup> group is located at the 5-position and is selected from propoxy, isopropoxy, tetrahydrofuran-3-yloxy, tetrahydropyran-4-yloxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 3-piperidinyloxy, N-methylpiperidin-3-yloxy, 4-piperidinyloxy, N-methylpiperidin-4-yloxy, N-allylpiperidin-4-yloxy, N-prop-2-ynylpiperidin-4-yloxy, N-acetylpiperidin-4-yloxy, N-methylsulphonylpiperidin-4-yloxy, piperidin-3-ylmethoxy, N-methylpiperidin-3-ylmethoxy, piperidin-4-ylmethoxy, N-methylpiperidin-4-ylmethoxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy,

or m is 2 and the first R<sup>1</sup> group is located at the 5-position and is selected from the group of substituents listed immediately above and the second R<sup>1</sup> group is located at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-[(3RS,4SR)-3,4-methylenedioxy-pyrrolidin-1-yl]ethoxy, 3-[(3RS,4SR)-3,4-methylenedioxy-pyrrolidin-1-yl]propoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy,

3-piperidinopropoxy, 2-piperidin-3-ylethoxy, 2-(N-methylpiperidin-3-yl)ethoxy,  
 3-piperidin-3-ylpropoxy, 3-(N-methylpiperidin-3-yl)propoxy, 2-piperidin-4-ylethoxy,  
 2-(N-methylpiperidin-4-yl)ethoxy, 3-piperidin-4-ylpropoxy, 3-(N-methylpiperidin-  
 4-yl)propoxy, 2-(1,2,3,6-tetrahydropyridin-1-yl)ethoxy, 3-(1,2,3,6-tetrahydropyridin-  
 5 1-yl)propoxy, 2-(4-hydroxypiperidin-1-yl)ethoxy, 3-(4-hydroxypiperidin-1-yl)propoxy,  
 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-1-ylbutoxy,  
 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 4-(4-methylpiperazin-  
 1-yl)butoxy, 2-(4-allylpiperazin-1-yl)ethoxy, 3-(4-allylpiperazin-1-yl)propoxy,  
 2-(4-prop-2-ynylpiperazin-1-yl)ethoxy, 3-(4-prop-2-ynylpiperazin-1-yl)propoxy,  
 10 2-(4-methylsulphonylpiperazin-1-yl)ethoxy, 3-(4-methylsulphonylpiperazin-1-yl)propoxy,  
 2-(4-acetylpiperazin-1-yl)ethoxy, 3-(4-acetylpiperazin-1-yl)propoxy, 4-(4-acetylpiperazin-  
 1-yl)butoxy, 2-(4-isobutyrylpiperazin-1-yl)ethoxy, 3-(4-isobutyrylpiperazin-1-yl)propoxy,  
 4-(4-isobutyrylpiperazin-1-yl)butoxy, 2-[4-(2-fluoroethyl)piperazin-1-yl]ethoxy,  
 3-[4-(2-fluoroethyl)piperazin-1-yl]propoxy, 2-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]ethoxy,  
 15 3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy, 2-(4-cyanomethylpiperazin-1-yl)ethoxy,  
 3-(4-cyanomethylpiperazin-1-yl)propoxy, 2-[2-(4-methylpiperazin-1-yl)ethoxy]ethoxy,  
 2-chloroethoxy, 3-chloropropoxy, 4-chlorobutoxy, 2-methylsulphonylethoxy,  
 3-methylsulphonylpropoxy, 2-(2-methoxyethoxy)ethoxy, 2-(4-pyridyloxy)ethoxy,  
 3-pyridylmethoxy and 2-cyanopyrid-4-ylmethoxy;

20 R<sup>a</sup> is chloro or bromo;

R<sup>b</sup> is hydrogen, chloro or methoxy; and

R<sup>d</sup> is methoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

25 7. A quinazoline derivative of the Formula I according to claim 1 wherein :-

Z is NH;

m is 2 and the first R<sup>1</sup> group is located at the 5-position and is selected from  
 isopropoxy and tetrahydropyran-4-yloxy, and the second R<sup>1</sup> group is located at the 7-position  
 and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-morpholinoethoxy,  
 30 3-morpholinopropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-(4-methylpiperazin-  
 1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy and  
 3-(4-acetylpiperazin-1-yl)propoxy; and

$R^a$  is chloro;

$R^b$  is hydrogen; and

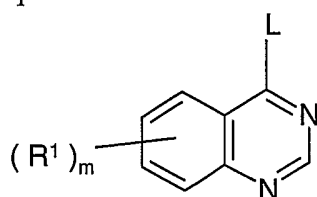
$R^d$  is methoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

5

8. A process for the preparation of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 which comprises :-

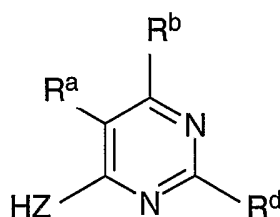
(a) for the production of those compounds of the Formula I wherein Z is an O, S or  $N(R^2)$  group, the reaction of a quinazoline of the Formula II



II

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wherein L is a displaceable group and m and  $R^1$  have any of the meanings defined in claim 1 except that any functional group is protected if necessary, with a compound of the Formula III



III

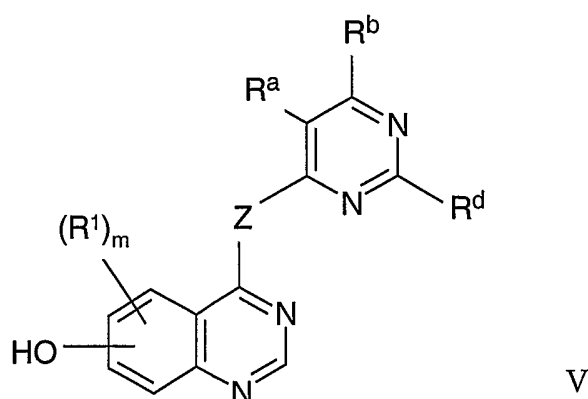
wherein Z is O, S, or  $N(R^2)$  and  $R^2$ ,  $R^a$ ,  $R^b$  and  $R^d$  have any of the meanings defined in claim 1

15 except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means;

(b) for the production of those compounds of the Formula I wherein at least one  $R^1$  group is a halogeno-(1-6C)alkoxy group or a group of the formula

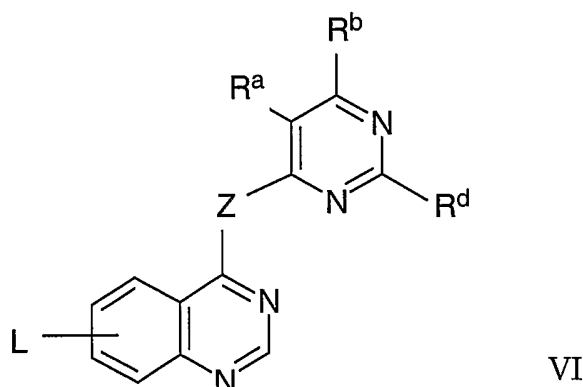


20 wherein  $Q^1$  is an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group or an optionally substituted alkyl group and  $X^1$  is an oxygen atom, the coupling of a quinazoline of the Formula V



wherein  $m$ ,  $R^1$ ,  $Z$ ,  $R^a$ ,  $R^b$  and  $R^d$  have any of the meanings defined in claim 1 except that any functional group is protected if necessary, with an appropriate alcohol wherein any functional group is protected if necessary whereafter any protecting group that is present is removed by  
 5 conventional means;

(c) for the production of those compounds of the Formula I wherein an  $R^1$  group contains a (1-6C)alkoxy or substituted (1-6C)alkoxy group or a (1-6C)alkylamino or substituted (1-6C)alkylamino group, the reaction of a quinazoline derivative of the Formula VI



10 wherein  $L$  is a displaceable group and  $Z$ ,  $R^a$ ,  $R^b$  and  $R^d$  have any of the meanings defined in claim 1 except that any functional group is protected if necessary, with an alcohol or amine as appropriate whereafter any protecting group that is present is removed by conventional means;

(d) for the production of those compounds of the Formula I wherein  $R^1$  is an amino-substituted (1-6C)alkoxy group, the reaction of a compound of the Formula I wherein  
 15  $R^1$  is a halogeno-substituted (1-6C)alkoxy group with a nitrogen-containing heterocyclyl compound or an appropriate amine;

(e) for the production of those compounds of the Formula I wherein  $R^1$  is an amino-hydroxy-disubstituted (1-6C)alkoxy group, the reaction of a compound of the Formula I wherein the  $R^1$  group contains an epoxy-substituted (1-6C)alkoxy group with a heterocyclyl

compound or an appropriate amine; or

(f) for the production of those compounds of the Formula I wherein Z is a SO or SO<sub>2</sub> group, the oxidation of a compound of Formula I wherein Z is a S group;

and when a pharmaceutically-acceptable salt of a quinazoline derivative of the

5 Formula I is required it may be obtained by reaction of said quinazoline derivative with a suitable acid using a conventional procedure.

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

10. The use of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 in the manufacture of a medicament for use as an anti-invasive agent in the containment and/or treatment of solid tumour disease.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB2004/002356

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D405/14 A61K31/517 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)

IPC 7 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, WPI Data, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                   | Relevant to claim No. |
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| X          | US 5 721 237 A (MYERS MICHAEL R ET AL)<br>24 February 1998 (1998-02-24)<br>column 2, line 9 - line 56; claim 1<br>-----                                              | 1-10                  |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

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- \*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
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- \*&\* document member of the same patent family

Date of the actual completion of the international search

24 August 2004

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB2004/002356

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