

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
16 December 2004 (16.12.2004)

PCT

(10) International Publication Number
WO 2004/108707 A1

(51) International Patent Classification⁷: **C07D 403/12**,
A61K 31/517, A61P 35/00

(74) Agent: **ASTRAZENECA**; Global Intellectual Property,
S-151 85 Sodertälje (SE).

(21) International Application Number:
PCT/GB2004/002365

(22) International Filing Date: 3 June 2004 (03.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
03291345.1 5 June 2003 (05.06.2003) EP

(71) Applicant (for all designated States except MG, US): **AS-
TRAZENECA AB** [SE/SE]; S-151 85 Sodertälje (SE).

(71) Applicant (for MG only): **ASTRAZENECA UK LIM-
ITED** [GB/GB]; 15 Stanhope Gate, London, Greater Lon-
don W1K 1LN (GB).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **BARLAAM, Bernard**
[FR/FR]; AstraZeneca Pharma, Z.I. La Pompelle, BP 1050,
F-51689 Reims Cedex 02 (FR).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

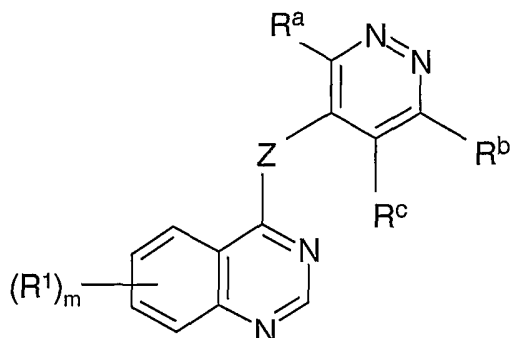
(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: PYRIDAZINIL QUINAZOLINE DERIVATIVES FOR USE IN THE TREATMENT OF TUMOURS



(I)

(57) Abstract: The invention concerns quina-
zoline derivatives of Formula (I) wherein Z is
an O, S, SO, SO₂, N(R²) or C(R²)(R³) group
wherein each R² or R³ group is hydrogen or
(1-8C)alkyl, m is 1, 2 or 3, each R¹ group has
any of the meanings defined in the description,
R^a is halogeno or (1-6C)alkoxy, R^b is
halogeno or (1-6C)alkoxy, and R^c is hydrogen,
halogeno, (1-8C)alkyl or (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.

QUINAZOLINE DERIVATIVES

The invention concerns certain novel quinazoline derivatives, or pharmaceutically-acceptable salts thereof, which possess anti-tumour activity and are accordingly useful in methods of treatment of the human or animal body. The invention also concerns processes for the manufacture of said 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.

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.

In recent years it has been discovered that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene *i.e.* a gene which, on activation, leads to the formation of malignant tumour cells (Bradshaw, Mutagenesis, 1986, 1, 91). Several such oncogenes give rise to the production of peptides which are receptors for growth factors. Activation of the growth factor receptor complex subsequently leads to an increase in cell proliferation. It is known, for example, that several oncogenes encode tyrosine kinase enzymes and that certain growth factor receptors are also tyrosine kinase enzymes (Yarden *et al.*, Ann. Rev. Biochem., 1988, 57, 443; Larsen *et al.*, Ann. Reports in Med. Chem., 1989, Chpt. 13). The first group of tyrosine kinases to be identified arose from such viral oncogenes, for example pp60^{v-Src} tyrosine kinase (otherwise known as v-Src), and the corresponding tyrosine kinases in normal cells, for example pp60^{c-Src} tyrosine kinase (otherwise known as c-Src).

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

includes Class I receptor tyrosine kinases comprising the EGF family of receptor tyrosine kinases such as the EGF, TGF α , Neu and erbB receptors, 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 α , PDGF β 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 Cancer, 1992, 28,
30 372-7), 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 regulate the assembly of focal adhesion complexes through interaction with a number of cytoplasmic proteins including, for example, focal adhesion kinase and paxillin. In addition c-Src is coupled to signalling pathways that regulate the actin cytoskeleton which facilitates cell motility. Likewise, important roles are played by the c-Src, c-Yes and c-Fyn non-receptor tyrosine kinases in integrin mediated signalling and in disrupting cadherin-dependent cell-cell junctions (Owens *et al.*, Molecular Biology of the Cell, 2000, 11, 51-64 and Klinghoffer *et al.*, EMBO Journal, 1999, 18, 2459-2471). Cellular motility is necessarily required for a localised tumour to progress through the stages of dissemination into the blood stream, invasion of other tissues and initiation of metastatic tumour growth. For example, colon tumour progression from localised to disseminated, invasive metastatic disease has been correlated with c-Src non-receptor tyrosine kinase activity (Brunton *et al.*, Oncogene, 1997, 14, 283-293, Fincham *et al.*, EMBO J, 1998, 17, 81-92 and Verbeek *et al.*, Exp. Cell Research, 1999, 248, 531-537).

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

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 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-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.

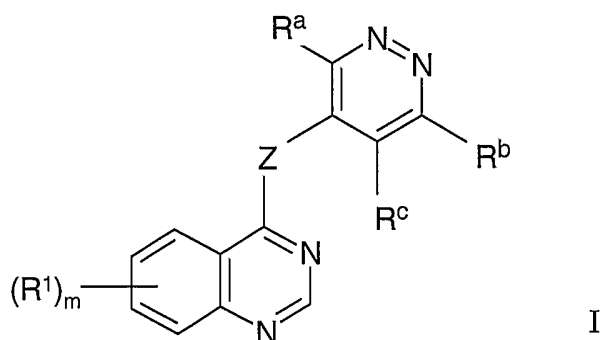
It is also known that c-Src non-receptor tyrosine kinase enzyme is involved in the control of osteoclast-driven bone resorption (Soriano *et al.*, Cell, 1991, 64, 693-702; Boyce *et al.*, J. Clin. Invest., 1992, 90, 1622-1627; Yoneda *et al.*, J. Clin. Invest., 1993, 91, 2791-2795 and Missbach *et al.*, Bone, 1999, 24, 437-49). An inhibitor of c-Src non-receptor
5 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.

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
10 (for example hepatic cirrhosis and lung fibrosis), glomerulonephritis, multiple sclerosis, psoriasis, hypersensitivity reactions of the skin, blood vessel diseases (for example atherosclerosis and restenosis), allergic asthma, insulin-dependent diabetes, diabetic retinopathy and diabetic nephropathy.

Generally the compounds of the present invention possess potent inhibitory activity
15 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 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
20 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, 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.

25 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. 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
30 therein of any 4-(pyridazinylamino)quinazoline derivatives.

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



wherein **Z** is an O, S, SO, SO₂, N(R²) or C(R²)(R³) group wherein each R² or R³ group, which may be the same or different, is hydrogen or (1-8C)alkyl;

m is 1, 2 or 3;

5 **each R¹ 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 Q^1-X^1-

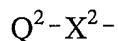
wherein X^1 is a direct bond or is selected from O, S, SO, SO_2 , $N(R^4)$, CO, $CH(OR^4)$, $CON(R^4)$, $N(R^4)CO$, $SO_2N(R^4)$, $N(R^4)SO_2$, $OC(R^4)_2$, $SC(R^4)_2$ and $N(R^4)C(R^4)_2$, wherein R^4 is hydrogen or (1-8C)alkyl, and Q^1 is aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl,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

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R⁵), CO, CH(OR⁵), CON(R⁵), N(R⁵)CO, SO₂N(R⁵), N(R⁵)SO₂, CH=CH and C≡C wherein R⁵ is hydrogen or (1-8C)alkyl or, when the inserted group is N(R⁵), R⁵ may also be

25 (2-6C)alkanoyl,

and wherein any $\text{CH}_2=\text{CH}-$ or $\text{HC}\equiv\text{C}-$ group within a R^1 substituent optionally bears at the terminal $\text{CH}_2=$ or $\text{HC}\equiv$ position a substituent selected from halogeno, carboxy, carbamoyl,

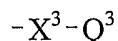
(1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the formula :



- 5 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

- 10 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, 15 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 :

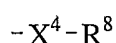


wherein X^3 is a direct bond or is selected from O, S, SO, SO_2 , $N(R^7)$, CO, $CH(OR^7)$, $CON(R^7)$, $N(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, $C(R^7)_2O$, $C(R^7)_2S$ and $N(R^7)C(R^7)_2$, wherein R^7 is hydrogen

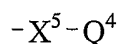
- 20 or (1-8C)alkyl, and Q^3 is aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, (3-8C)cycloalkenyl, (3-8C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

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

- 25 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, 30 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-(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,
 5 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
 10 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 halogeno or (1-6C)alkoxy;

15 R^b is halogeno or (1-6C)alkoxy; and

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

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
 20 (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
 25 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,
 30 and di-[(1-6C)alkyl]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.

10 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 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, 5 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 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, 10 (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 R¹ substituents may only be located at the 5-, 6-, 7- or 8-positions on the quinazoline ring *i.e.* that the 2-position remains unsubstituted.

15 Suitable values for any of the 'R' groups (R^a, R^b, R^c and R¹ to R¹⁰) or for various groups within an R¹ substituent include:-

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

- for (1-6C)alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;
- for N-(1-6C)alkylcarbamoyl: N-methylcarbamoyl, N-ethylcarbamoyl and N-propylcarbamoyl;
- 5 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: acetoxyl and propionyloxy;
- for (2-6C)alkanoylamino: acetamido and propionamido;
- 10 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;
- for N-(1-6C)alkyl-(1-6C)alkanesulphonylamino: N-methylmethanesulphonylamino and
- 15 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;
- for N-(1-6C)alkyl-(3-6C)alkynoylamino: N-methylpropiolamido;
- 20 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, 2-ethylaminoethyl and 3-methylaminopropyl;
- 25 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, 1-chloroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl, 3-chloropropyl, 3,3-difluoropropyl and 3,3,3-trifluoropropyl;
- 30 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;
for cyano-(1-6C)alkyl: cyanomethyl, 2-cyanoethyl, 1-cyanoethyl and
5 3-cyanopropyl;
for (2-6C)alkanoylamino-(1-6C)alkyl: acetamidomethyl, propionamidomethyl and
2-acetamidoethyl; and
for (1-6C)alkoxycarbonylamino-(1-6C)alkyl: methoxycarbonylaminomethyl,
ethoxycarbonylaminomethyl,
10 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, ethylenedioxy, isopropylidenedioxy or ethylenedioxy and the oxygen atoms thereof occupy
15 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 attached to the Q^1 group. Similarly, when, for example a CH_3 group within a R^1 substituent
20 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 -.

As defined hereinbefore, adjacent carbon atoms in any (2-6C)alkylene chain within a
25 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 rise to, for example, a 2-(2-methoxyacetamido)ethoxy group.

30 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]carbamoylethynyl groups such as N-(2-pyrrolidin-1-ylethyl)carbamoylethynyl or N-[heterocyclyl-(1-6C)alkyl]carbamoylethynyl groups such as N-(2-pyrrolidin-1-ylethyl)carbamoylethynyl.

5 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
 10 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
 15 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
 20 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
 25 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
 30 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

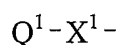
CH₂ or CH₃ group therein by one of the hereinbefore defined substituents therefor. For example, if R¹ includes a heteroaryl group that is substituted by, for example, a (1-6C)alkylamino-(1-6C)alkyl group, the terminal CH₃ group of the (1-6C)alkylamino group may be further substituted by, for example, a (1-6C)alkylsulphonyl group or a (2-6C)alkanoyl group. For example, the R¹ group may be a heteroaryl group such as a thienyl group that is substituted by a N-(2-methylsulphonyl)ethyl)aminomethyl group such that R¹ is, for example, a 5-[N-(2-methylsulphonyl)ethyl)aminomethyl]thien-2-yl group. Further, for example, if R¹ includes a heterocyclyl group such as a piperidinyl or piperazinyl group that is substituted on a nitrogen atom thereof by, for example, a (2-6C)alkanoyl group, the terminal CH₃ group of the (2-6C)alkanoyl group may be further substituted by, for example, a di-[(1-6C)alkyl]amino group. For example, the R¹ group may be a 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, R¹, R^a, R^b and R^c has any of the meanings defined hereinbefore or in paragraphs (a) to (s) hereinafter :-

- (a) Z is O, S, SO, SO₂, CH₂ or NH;
- (b) Z is O;
- (c) Z is NH;
- (d) m is 1 or 2, and each R¹ 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,

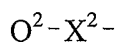
and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, $N(R^5)$, $CON(R^5)$, $N(R^5)CO$, $CH=CH$ and $C\equiv C$ wherein R^5 is hydrogen or (1-8C)alkyl, or, when the
10 inserted group 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,

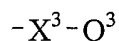
(1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl or from a group of the

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 :

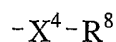


25 wherein X^3 is a direct bond or is selected from O, $N(R^7)$, $CON(R^7)$, $N(R^7)CO$ and $C(R^7)_2O$, wherein R^7 is hydrogen or (1-8C)alkyl, and Q^3 is heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

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

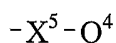
30 halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy, (1-6C)alkylsulphonyl, N-(1-6C)alkylcarbamoyl,

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 :

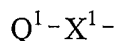


- 10 wherein X^5 is a direct bond or is selected from O, N(R^{10}) and CO, wherein R^{10} is hydrogen or (1-8C)alkyl, and Q^4 is heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-8C)alkyl and (1-6C)alkoxy,

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 :

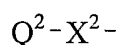


- 25 wherein X^1 is a direct bond or is selected from O, NH, CONH, NHCO and OCH₂ and Q^1 is phenyl, benzyl, cyclopropylmethyl, 2-thienyl, 1-imidazolyl, 1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, 2-, 3- or 4-pyridyl, 2-imidazol-1-ylethyl, 3-imidazol-1-ylpropyl, 2-(1,2,3-triazolyl)ethyl, 3-(1,2,3-triazolyl)propyl, 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 R¹ 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,

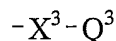
and wherein any CH₂=CH- or HC≡C- group within a R¹ substituent optionally bears at
 15 the terminal CH₂= or HC≡ position a substituent selected from carbamoyl,
N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N,N-dimethylcarbamoyl,
 aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl, methylaminomethyl,
 2-methylaminoethyl, 3-methylaminopropyl, 4-methylaminobutyl, dimethylaminomethyl,
 2-dimethylaminoethyl, 3-dimethylaminopropyl or 4-dimethylaminobutyl, or from a group of
 20 the formula :



wherein X² is a direct bond or is CO, NHCO or N(Me)CO and Q² 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,

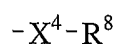
and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each
 said CH₂ or CH₃ group one or more fluoro or chloro groups or a substituent selected from

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 :



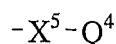
- 5 wherein X^3 is a direct bond or is selected from O, NH, CONH, NHCO and CH_2O and Q^3 is pyridyl, pyridylmethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, piperidin-3-ylmethyl, 10 2-piperidin-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 R¹ optionally bears 1 or 2 oxo substituents;

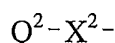
- (f) m is 1 and the R¹ group is located at the 5-, 6- or 7-position or m is 2 and the R¹ groups, which may be the same or different, are located at the 5- and 7-positions or at the 6- and 7-positions and each R¹ is selected from hydroxy, amino, methyl, ethyl, propyl, butyl, vinyl, ethynyl, methoxy, 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 R¹ 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 R¹ is a vinyl or ethynyl group, the R¹ substituent optionally bears at the terminal CH₂= 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 X² is a direct bond or is NHCO or N(Me)CO and Q² 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, 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 CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ 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, acetoxo, acetamido and N-methylacetamido,

- and wherein any phenyl, imidazolyl, triazolyl, pyridyl or heterocyclyl group within a substituent on R¹ 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 R¹ 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 R¹ optionally bears 1 or 2 oxo substituents;

(g) m is 1 and the R¹ group is located at the 7-position or m is 2 and the R¹ groups, which may be the same or different, are located at the 6- and 7-positions and each R¹ 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 R¹ 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 CH₂ or CH₃ group within a R¹ substituent optionally bears on each 30 said CH₂ or CH₃ 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 R¹ 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, 5 piperazin-1-yl or homopiperazin-1-yl group within a R¹ 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 R¹ optionally bears 1 or 2 oxo substituents;

- 10 (h) m is 1 and the R¹ group is located at the 5-position or m is 2 and the R¹ groups, which may be the same or different, are located at the 5- and 7-positions and each R¹ 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 R¹ substituent 25 are optionally separated by the insertion into the chain of a group selected from O, NH, CH=CH and C≡C,

- and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ 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 acetoxy,

and wherein any heterocyclyl group within a substituent on R¹ 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 R¹ 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 R¹ optionally bears 1 or 2 oxo substituents;

- (i) m is 2 and the R¹ groups, which may be the same or different, are located at the 6- and 7-positions and the R¹ group at the 6-position is selected from hydroxy, methoxy, ethoxy and
 10 propoxy, and the R¹ 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 CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ 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 R¹ 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 R¹ 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 R¹ optionally bears 1 or 2 oxo substituents;

- (j) m is 2 and the R¹ groups, which may be the same or different, are located at the 5- and 7-positions and the R¹ 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 R¹ 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 CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ 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 R¹ 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 R¹ 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 R¹ optionally bears 1 or 2 oxo substituents;
- (k) R^a is fluoro, chloro, bromo, methoxy or ethoxy;
- (l) R^a is fluoro, chloro or bromo;
- (m) R^a is chloro or bromo;
- (n) R^b is fluoro, chloro, bromo, methoxy or ethoxy;
- (o) R^b is methoxy or ethoxy;

- (p) R^b is methoxy;
- (q) R^c is hydrogen, fluoro, chloro, bromo, methyl, ethyl, methoxy or ethoxy;
- (r) R^c is hydrogen, fluoro, chloro, bromo, methoxy or ethoxy; and
- (s) R^c is hydrogen.

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^c 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^c has any of the meanings defined hereinbefore and :-

R^a is halogeno and R^b 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 R¹ group is located at the 5-, 6- or 7-position or m is 2 and the R¹ 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 R¹ 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,

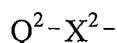
4-piperazin-1-ylbutylamino, 2-homopiperazin-1-ylethylamino or
3-homopiperazin-1-ylpropylamino,

and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ 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 R¹ is a vinyl or ethynyl group, the R¹ substituent optionally bears at the terminal CH₂= 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 X² is a direct bond or is NHCO or N(Me)CO and Q² 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 CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ 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 R¹ 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 R¹ 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 R¹ optionally bears 1 or 2
10 oxo substituents;

R^a is fluoro, chloro, bromo, methoxy or ethoxy;

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

R^c is hydrogen;

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 R¹ groups, which may be the same or different, are located at the 6- and 7-positions and the R¹ group at the 6-position is selected from hydroxy, methoxy, ethoxy and
20 propoxy, and the R¹ 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 CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ 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 R¹ 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 R¹ 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 R¹ optionally bears 1 or 2 oxo substituents;

R^a is chloro or bromo;

R^b is methoxy or ethoxy; and

R^c is hydrogen;

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 R¹ group is a 6-methoxy group and the second R¹ 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 methoxy; and

R^c is hydrogen;

- 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-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 methoxy; and

R^c is hydrogen;

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 R¹ groups, which may be the same or different, are located at the 5- and 7-positions and the R¹ 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 R¹ 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 CH₂ or CH₃ group within a R¹ substituent optionally bears on each
20 said CH₂ or CH₃ 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 R¹ optionally bears 1 or 2
25 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 R¹ 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 R¹ optionally bears 1 or 2 oxo substituents;

R^a is fluoro, chloro, bromo, methoxy or ethoxy;

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

R^c is hydrogen;

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-acetyl piperidin-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-methylenedioxypyrrolidin-1-yl]ethoxy, 3-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-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 fluoro, chloro or bromo;

R^b is methoxy or ethoxy; and

R^c is hydrogen;

- 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 R¹ 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 R¹ group is located at the 5-position and is selected from the
 group of substituents listed immediately above and the second R¹ 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 methoxy; and

R^c is hydrogen;

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-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-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;

R^b is methoxy; and

R^c is hydrogen;

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 methoxy; and

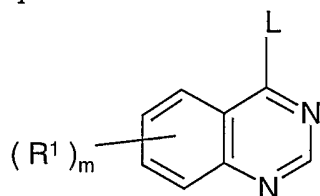
R^c is hydrogen;

or a pharmaceutically-acceptable acid-addition salt thereof.

Particular compounds of the invention are, for example, the quinazoline derivatives of the Formula I that are disclosed within the Examples hereinafter.

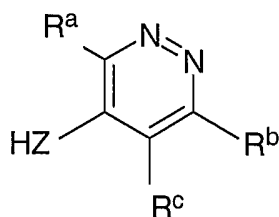
A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a quinazoline derivative of the Formula I are provided as a further feature of the invention and are illustrated by the following representative process variants in which, unless otherwise stated, Z, m, R¹, R^a, R^b and R^c have any of the meanings defined hereinbefore. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and within the accompanying Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

- (a) For the production of those compounds of the Formula I wherein Z is an O, S or N(R²) group, the reaction of a quinazoline of the Formula II



II

wherein L is a displaceable group and m and R¹ have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with a compound of the Formula III



III

wherein Z is O, S, or N(R²) and R², R^a, R^b and R^c have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

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

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

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 10 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 15 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, conveniently in the presence of a base, for example potassium carbonate or sodium 20 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 the formula H-L wherein L has the meaning defined hereinbefore. When it is desired to obtain 25 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-methyldmorpholine 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.

30 Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as

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

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

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

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

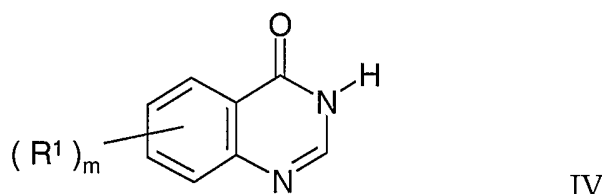
Examples of amino protecting groups include formyl, aryl-lower alkyl groups (for example benzyl and substituted benzyl, 4-methoxybenzyl, 2-nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-4-anisylmethyl and furylmethyl groups; lower

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

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

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

Quinazoline starting materials of the Formula II may be obtained by conventional
15 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



wherein m and R¹ 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
20 chloride, phosphoryl chloride or a mixture of carbon tetrachloride and triphenylphosphine whereafter any protecting group that is present is removed by conventional means.

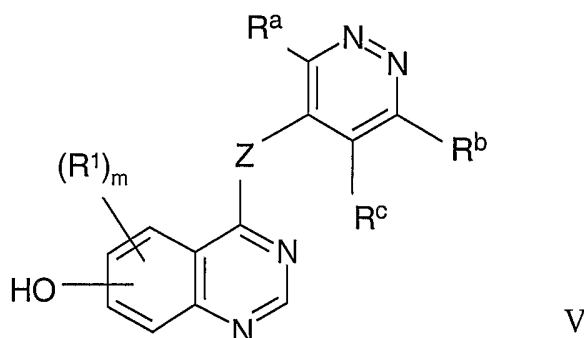
The 4-chloroquinazoline so obtained may be converted, if required, into a 4-pentafluorophenoxyquinazoline by reaction with pentafluorophenol in the presence of a suitable base such as potassium carbonate and in the presence of a suitable solvent such as
25 N,N-dimethylformamide.

4-Aminopyridazine starting materials (Formula III, for example when Z is NH) may be obtained by conventional procedures as illustrated in the Examples. Corresponding 4-hydroxy- and 4-mercaptopyridazine 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^1 group is a halogeno-(1-6C)alkoxy group or a group of the formula



wherein Q^1 is an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-
 5 (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, conveniently in the presence of a suitable dehydrating agent, of a quinazoline of the Formula V

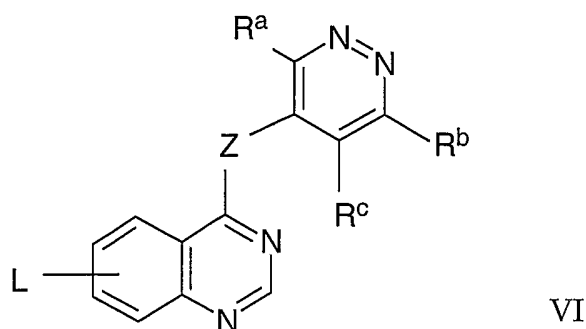


wherein m , R^1 , Z , R^a , R^b and R^c have any of the meanings defined hereinbefore except that any
 10 functional group is protected if necessary, with an appropriate alcohol wherein any functional group is protected if necessary whereafter any protecting group that is present is removed by conventional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

A suitable dehydrating agent is, for example, a carbodiimide reagent such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or a mixture of
 15 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 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.

20 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 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
 25 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 defined hereinbefore, of a quinazoline derivative of the Formula VI



wherein L is a displaceable group as defined hereinbefore and Z, R^a, R^b and R^c 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 R¹ 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 R¹ 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 R¹ 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 R¹ group contains an epoxy-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate amine.

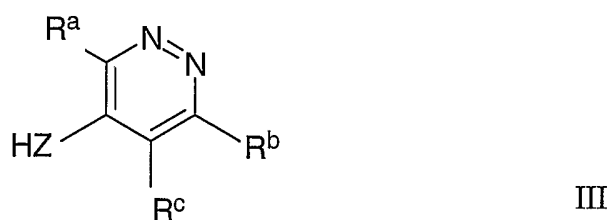
The reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near ambient temperature.

(f) For the production of those compounds of the Formula I wherein Z is a SO or SO₂
 25 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



wherein Z is O, S, or N(R²) and R², R^a, R^b and R^c have any of the meanings defined
10 hereinbefore are novel compounds. For example, although 4-aminopyridazine 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-3-chloro-6-methoxypyridazine 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.

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 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 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 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 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 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 1.5×10^4 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% CO₂ : 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% CO₂ : 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 IC₅₀ 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 (Difco
10 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 2×10^7 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% CO₂ : 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 IC₅₀ 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 5×10^6 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):-

- 10 Test (a):- IC_{50} in the range, for example, 0.001 - 10 μM ;
Test (b):- IC_{50} in the range, for example, 0.1 - 20 μM ;
Test (c):- activity in the range, for example, 0.1-25 μM ;
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 μM ;
Test (b):- IC_{50} in the range, for example, 0.1 - 5 μM ;
Test (c):- activity in the range, for example, 0.1-5 μM ;
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 0.04 μM .

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 are expected when a compound of Formula I, or a pharmaceutically-acceptable salt thereof, as
25 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-acceptable diluent or carrier.

30 The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a

finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

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

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

20 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 administration, a dose in the range, for example, 0.1 mg/kg to 30 mg/kg body weight will
25 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.

 According to a further aspect of the invention there is provided a quinazoline derivative
30 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 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
5 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 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.
10 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 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
15 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 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
20 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 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
25 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.

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
30 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 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.

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

10 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 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
15 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-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
20 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 hereinbefore in the manufacture of a medicament for use in providing a c-Src kinase inhibitory
25 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 radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents :-

- 30 (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 α -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 [HerceptinTM] 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 [AvastinTM], 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, WO 01/92224, WO 02/04434 and WO 02/08213;
- (vii) antisense therapies, for example those which are directed to the targets listed above,
5 such as ISIS 2503, an anti-ras antisense;
- (viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or
10 radiotherapy such as multi-drug resistance gene therapy; and
- (ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as
15 cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within the dosage range described hereinbefore and
20 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 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
25 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.

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
30 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 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
5 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 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
10 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 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
15 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 thin layer chromatographic, HPLC, infra-red (IR) and/or NMR analysis;

(vii) melting points are uncorrected and were determined using a Mettler SP62
20 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;

(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
25 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:-

DMF	<u>N,N</u> -dimethylformamide
DMSO	dimethylsulphoxide
THF	tetrahydrofuran

Example 1**4-(3-chloro-6-methoxypyridazin-4-ylamino)-5-isopropoxy-7-(2-morpholinoethoxy)quinazoline**

Sodium hexamethyldisilazane (1M solution in THF; 0.57 ml) was added dropwise to a mixture of 4-amino-3-chloro-6-methoxypyridazine (0.045 g), 4-chloro-5-isopropoxy-7-(2-morpholinoethoxy)quinazoline (0.1 g) and THF (1.5 ml) that had been cooled to 0°C. The resultant mixture was stirred at 0°C for 15 minutes, allowed to warm to ambient temperature and stirred at ambient temperature for 2 hours. Acetic acid (0.05 ml) was added and the resultant mixture was evaporated. The mixture was partitioned between methylene chloride and a saturated aqueous sodium bicarbonate solution. The organic layer was washed with water, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained the title compound as a solid (0.09 g); NMR Spectrum: (CDCl₃) 1.58 (s, 3H), 1.59 (s, 3H), 2.6 (m, 4H), 2.87 (m, 2H), 3.76 (m, 4H), 4.14 (s, 3H), 4.25 (m, 2H), 4.91 (m, 1H), 6.67 (s, 1H), 6.89 (s, 1H), 8.7 (m, 2H); Mass Spectrum: M+H⁺ 475 and 477.

The 4-chloro-5-isopropoxy-7-(2-morpholinoethoxy)quinazoline that was used as a starting material was prepared as follows :-

Sodium hydride (60% dispersion in mineral oil; 1 g) was added portionwise to a solution of isopropanol (1.25 g) in DMF (20 ml) that had been cooled to 5°C. The resultant mixture was allowed to warm to ambient temperature and was stirred for 15 minutes. The mixture was recooled to 5°C and 5,7-difluoro-3,4-dihydroquinazolin-4-one (International Patent Application WO 01/94341; 2 g) was added portionwise. The mixture was stirred at ambient temperature for 30 minutes. The mixture was poured into water (200 ml) and, with vigorous stirring, glacial acetic acid was added to acidify the mixture to pH4. The resultant solid was isolated, washed with water and with diethyl ether and dried under vacuum. There was thus obtained 7-fluoro-5-isopropoxy-3,4-dihydroquinazolin-4-one (1.75 g); NMR Spectrum: (DMSO-d₆) 1.31 (s, 6H), 4.73 (m, 1H), 6.89 (m, 1H), 6.95 (m, 1H), 7.96 (s, 1H); Mass Spectrum: M+H⁺ 223.

A mixture of 7-fluoro-5-isopropoxy-3,4-dihydroquinazolin-4-one (1 g), 2-morpholinoethanol (0.71 g), potassium *tert*-butoxide (3 g) and THF (40 ml) was stirred and heated to reflux for 18 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was purified by column chromatography on a

Waters Symmetry column (C18 reversed-phase, 5 microns, 20 mm diameter, 100 mm length; Waters Inc., Milford, MA01757, USA) using decreasingly polar mixtures of water (containing 5% methanol and 1% acetic acid) and acetonitrile as eluent. The material so obtained was stirred under a 7M methanolic ammonia solution (20 ml) for 5 minutes. The mixture was
5 evaporated and the residue was stirred under methylene chloride. The mixture was filtered and the filtrate was evaporated. There was thus obtained 5-isopropoxy-7-(2-morpholinoethoxy)-3,4-dihydroquinazolin-4-one (0.876 g); Mass Spectrum: $M+H^+$ 334.

A mixture of the material so obtained, triphenylphosphine (1.72 g), carbon tetrachloride (0.89 ml) and 1,2-dichloroethane (50 ml) was stirred and heated to 70°C for
10 2 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 as eluent. There was thus obtained 4-chloro-5-isopropoxy-7-(2-morpholinoethoxy)quinazoline as an oil which crystallised on standing (0.8 g); NMR Spectrum: ($CDCl_3$) 1.48 (s, 3H), 1.49 (s, 3H), 2.59 (m, 4H), 2.87 (t, 2H), 3.76 (m, 4H), 4.26 (d,
15 2H), 4.72 (m, 1H), 6.62 (s, 1H), 6.91 (s, 1H), 8.79 (s, 1H); Mass Spectrum: $M+H^+$ 352 and 354.

The 4-amino-3-chloro-6-methoxypyridazine that was used as a starting material was prepared as follows :-

Using a cold water bath to prevent the temperature of the reaction mixture from rising
20 above 40 to 45°C, potassium dichromate (43 g) was added portionwise over 30 minutes to a mechanically stirred mixture of 3,6-dichloro-4-methylpyridazine (T. Kuraishi, Pharm. Bull. (Tokyo), 1957, 5, 587; 20 g) and concentrated sulphuric acid (125 ml). The resultant mixture was stirred at ambient temperature for 2 hours. The mixture was poured onto a mixture of ice and water and extracted with diethyl ether (3 x 500 ml). The organic layer was separated and
25 evaporated. The residue was partitioned between diethyl ether and a 5% aqueous sodium bicarbonate solution. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ethyl acetate (3 x 200 ml). The organic solution was washed with brine, dried over magnesium sulphate and evaporated. There was thus obtained 3,6-dichloropyridazine-4-carboxylic acid (containing some 6-chloro-3-hydroxypyridazine-
30 4-carboxylic acid) as a white solid (18.4 g); NMR Spectrum: ($DMSO-d_6$) 8.32 (s, 1H); ^{13}C NMR Spectrum: ($DMSO-d_6$) 130.8, 134.9, 152.8, 157, 163.8; Mass Spectrum: $M+H^+$ 193.

A mixture of a portion (10 g) of the material so obtained, concentrated sulphuric acid (10 drops) and anhydrous ethanol (50 ml) was heated to reflux for 24 hours. The mixture was

evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was dried over magnesium sulphate and evaporated. The residue was dissolved in phosphoryl chloride (70 ml) and the solution was heated to 70°C for 2 hours. The resultant mixture was cooled to ambient temperature, poured onto a mixture of ice and water and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 4:1 mixture of petroleum ether (b.p 40-60°C) and ethyl acetate as eluent. There was thus obtained ethyl 3,6-dichloropyridazine-4-carboxylate as an oil (5.7 g); NMR Spectrum: (CDCl₃) 1.45 (t, 3H), 4.49 (q, 2H), 7.87 (s, 1H); Mass Spectrum: M+H⁺ 221.

Sodium methoxide (0.735 g) was added portionwise over 15 minutes to a stirred mixture of ethyl 3,6-dichloropyridazine-4-carboxylate (3 g) and methanol (40 ml) and the resultant mixture was stirred at ambient temperature for 3 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic solution was dried over magnesium sulphate and evaporated. A mixture of the solid so obtained and a cooled 30% aqueous ammonium hydroxide solution (18 ml) was stirred at 0°C for 24 hours. The solid so obtained was isolated, washed with a small volume of water and dried under vacuum in the presence of phosphorus pentoxide. The solid was purified by column chromatography using a Waters Symmetry column (C18 reversed-phase, 5 microns, 20 mm diameter, 100 mm length) and decreasingly polar mixtures of water (containing 5% methanol and 1% acetic acid) and acetonitrile as eluent. There were so obtained in turn :-
3-chloro-6-methoxypyridazine-4-carboxamide (0.342 g); NMR Spectrum: (DMSO-d₆) 4.05 (s, 3H), 7.43 (s, 1H), 8.03 (br s, 1H), 8.2 (br s, 1H); Mass Spectrum: M+H⁺ 188;
3,6-dichloropyridazine-4-carboxamide (0.164 g); NMR Spectrum: (DMSO-d₆) 8.19 (br s, 1H), 8.22 (s, 1H), 8.27 (br s, 1H); Mass Spectrum: M+H⁺ 192; and
6-chloro-3-methoxypyridazine-4-carboxamide (0.634 g); NMR Spectrum: (DMSO-d₆) 4.1 (s, 3H), 7.93 (s, 1H), 8.0 (br s, 1H), 8.04 (br s, 1H); Mass Spectrum: M+H⁺ 188.

Bromine (0.091 ml) was added dropwise to an ice-cooled 2N aqueous sodium hydroxide solution (3.5 ml) and the mixture was stirred for 2 minutes. 3-Chloro-6-methoxypyridazine-4-carboxamide (0.332 g) was added and the mixture was stirred at ambient temperature for 2 hours and then heated to 70°C for 2 hours. The mixture was cooled to ambient temperature and extracted with ethyl acetate. The organic layer was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on

silica using a 10:3 mixture of methylene chloride and ethyl acetate as eluent. There were thus obtained in turn 4-amino-5-bromo-3-chloro-6-methoxypyridazine (0.075 g); NMR Spectrum: (CDCl₃) 4.14 (s, 3H), 5.07 (br s, 2H); ¹³C NMR Spectrum: (CDCl₃) 56.1, 96.2, 139.1, 142.6, 161.7; Mass Spectrum: M+H⁺ 238; and the required 4-amino-3-chloro-6-methoxypyridazine
5 (0.045 g); NMR Spectrum: (CDCl₃) 4.04 (s, 3H), 4.66 (br s, 2H), 6.17 (s, 1H); ¹³C NMR Spectrum: (CDCl₃) 55, 97.3, 141.1, 144.1, 160; Mass Spectrum: M+H⁺ 160.

Example 2

4-(6-chloro-3-methoxypyridazin-4-ylamino)-5-isopropoxy-

10 **7-(3-morpholinopropoxy)quinazoline**

Using an analogous procedure to that described in Example 1, 4-amino-6-chloro-3-methoxypyridazine (0.066 g) was reacted with 4-chloro-5-isopropoxy-7-(3-morpholinopropoxy)quinazoline (0.152 g) to give the title compound as a solid in 70% yield; NMR Spectrum: (CDCl₃) 1.59 (s, 3H), 1.6 (s, 3H), 2.04 (m, 2H), 2.49 (m, 4H), 2.55 (m,
15 2H), 3.73 (m, 4H), 4.18 (m, 2H), 4.26 (s, 3H), 4.90 (m, 1H), 6.6 (s, 1H), 6.9 (s, 1H), 8.76 (s, 1H), 9.12 (s, 1H); Mass Spectrum: M+H⁺ 489 and 491.

The 4-chloro-5-isopropoxy-7-(3-morpholinopropoxy)quinazoline 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 :-

20 Using sodium tert-pentoxide in place of potassium tert-butoxide, 7-fluoro-5-isopropoxy-3,4-dihydroquinazolin-4-one was reacted with 3-morpholinopropanol (Bull. Soc. Chim. Fr., 1962, 1117) to give 5-isopropoxy-7-(3-morpholinopropoxy)-3,4-dihydroquinazolin-4-one in 23% yield; NMR Spectrum: (CDCl₃) 1.46 (s, 3H), 1.47 (s, 3H), 2.03 (m, 2H), 2.51 (m, 4H), 2.56 (m, 2H), 3.74 (m, 4H), 4.13 (m, 2H), 4.63 (m, 1H), 6.49
25 (s, 1H), 6.74 (s, 1H), 7.95 (s, 1H); Mass Spectrum: M+H⁺ 348.

The material so obtained was reacted with carbon tetrachloride and triphenylphosphine to give 4-chloro-5-isopropoxy-7-(3-morpholinopropoxy)quinazoline in 59% yield; NMR Spectrum: (CDCl₃) 1.48 (s, 3H), 1.5 (s, 3H), 2.04 (m, 2H), 2.48 (m, 4H), 2.55 (t, 2H), 3.73 (m, 4H), 4.19 (t, 2H), 4.72 (m, 1H), 6.58 (s, 1H), 6.92 (s, 1H), 8.78 (s, 1H).

30 The 4-amino-6-chloro-3-methoxypyridazine that was used as a starting material was prepared as follows :-

Bromine (0.464 g) was added dropwise to an ice-cooled 2N aqueous sodium hydroxide solution (5.8 ml) and the mixture was stirred for 2 minutes. 6-Chloro-

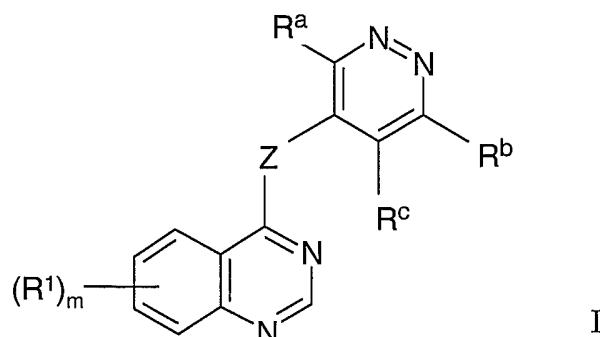
3-methoxypyridazine-4-carboxamide (0.544 g) was added and the mixture was stirred at ambient temperature for 1 hour and then heated to 70°C for 4 hours. The mixture was cooled to ambient temperature and extracted with ethyl acetate. The organic layer was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 10:3 mixture of methylene chloride and ethyl acetate as eluent. There were thus obtained in turn 4-amino-5-bromo-6-chloro-3-methoxypyridazine (0.16 g); Mass Spectrum: $M+H^+$ 238; and the required 4-amino-6-chloro-3-methoxypyridazine (0.068 g); NMR Spectrum: (DMSO_d₆) 3.98 (s, 3H), 6.54 (s, 1H), 6.62 (br s, 2H); ¹³C NMR Spectrum: (DMSO_d₆) 55, 106.1, 140.1, 150.5, 155.4; Mass Spectrum: $M+H^+$ 160.

10

15

CLAIMS

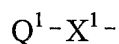
1. A quinazoline derivative of the Formula I



- 5 wherein **Z** is an O, S, SO, SO₂, N(R²) or C(R²)(R³) group wherein each R² or R³ group, which may be the same or different, is hydrogen or (1-8C)alkyl;

m is 1, 2 or 3;

- each R¹ group**, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, (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 :

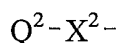


- wherein X¹ is a direct bond or is selected from O, S, SO, SO₂, N(R⁴), CO, CH(OR⁴), CON(R⁴), N(R⁴)CO, SO₂N(R⁴), N(R⁴)SO₂, OC(R⁴)₂, SC(R⁴)₂ and N(R⁴)C(R⁴)₂, wherein R⁴ is hydrogen or (1-8C)alkyl, and Q¹ is aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, (3-8C)cycloalkenyl, (3-8C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl, or (R¹)_m is (1-3C)alkylenedioxy,

- and wherein adjacent carbon atoms in any (2-6C)alkylene chain within a R¹ substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO₂, N(R⁵), CO, CH(OR⁵), CON(R⁵), N(R⁵)CO, SO₂N(R⁵), N(R⁵)SO₂, CH=CH and C≡C wherein

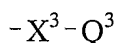
R⁵ is hydrogen or (1-8C)alkyl or, when the inserted group is N(R⁵), R⁵ may also be (2-6C)alkanoyl,

and wherein any CH₂=CH- or HC≡C- group within a R¹ substituent optionally bears at the terminal CH₂= or HC≡ 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 X² is a direct bond or is selected from CO and N(R⁶)CO, wherein R⁶ is hydrogen or (1-8C)alkyl, and Q² is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

and wherein any CH₂ or CH₃ group within a R¹ substituent optionally bears on each said CH₂ or CH₃ 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 X³ is a direct bond or is selected from O, S, SO, SO₂, N(R⁷), CO, CH(OR⁷), CON(R⁷), N(R⁷)CO, SO₂N(R⁷), N(R⁷)SO₂, C(R⁷)₂O, C(R⁷)₂S and N(R⁷)C(R⁷)₂, wherein R⁷ is hydrogen or (1-8C)alkyl, and Q³ is aryl, aryl-(1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-6C)alkyl, (3-8C)cycloalkenyl, (3-8C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

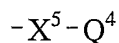
and wherein any aryl, heteroaryl or heterocyclyl group within a R¹ substituent optionally bears 1, 2 or 3 substituents, which may be the same or different, selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl, (1-6C)alkoxy,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

10 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
15 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 halogeno or (1-6C)alkoxy;

20 R^b is halogeno or (1-6C)alkoxy; and

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

or a pharmaceutically-acceptable salt thereof.

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

25 each of Z, m, R^1 and R^c has any of the meanings defined in claim 1, R^a is halogeno and R^b 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 CH₂ or CH₃ group within a R¹ substituent optionally bears on each
 said CH₂ or CH₃ 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 R¹ optionally bears 1 or 2
 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl,
 hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidenedioxy 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 R¹ 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 R¹ optionally bears 1 or 2
 oxo substituents;

R^a is chloro or bromo;

25 R^b is methoxy or ethoxy; and

R^c is hydrogen;

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 R¹ group is a 6-methoxy group and the second R¹ 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 methoxy; and
 R^c is hydrogen;

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 R¹ 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 R¹ 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 R¹ optionally bears 1 or 2 oxo substituents;

R^a is fluoro, chloro, bromo, methoxy or ethoxy;

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

R^c is hydrogen;

- 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 R¹ 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 R¹ group is located at the 5-position and is selected from the group of substituents listed immediately above and the second R¹ 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^a is chloro or bromo;

R^b is methoxy; and

R^c is hydrogen;

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^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 and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy,

30 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,
 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,
 5 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

R^a is chloro;

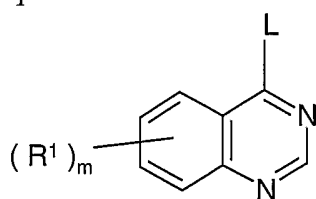
R^b is methoxy; and

R^c is hydrogen;

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

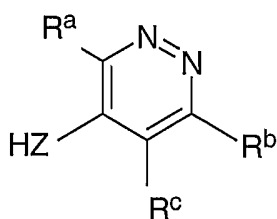
8. A process for the preparation of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 which comprises :-

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



II

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



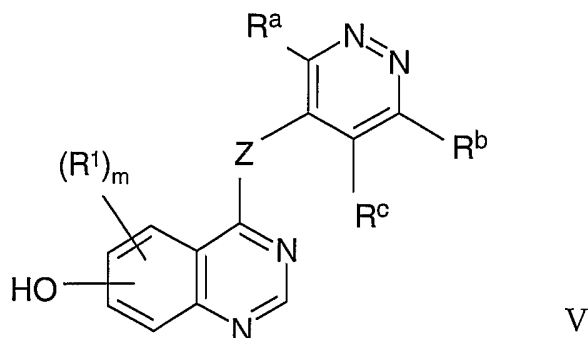
III

- 20 wherein Z is O, S, or $N(R^2)$ and R^2 , R^a , R^b and R^c have any of the meanings defined in claim 1 except that any functional group is protected if necessary, whereafter any protecting group that is present is removed 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

- 25 Q^1-X^1-

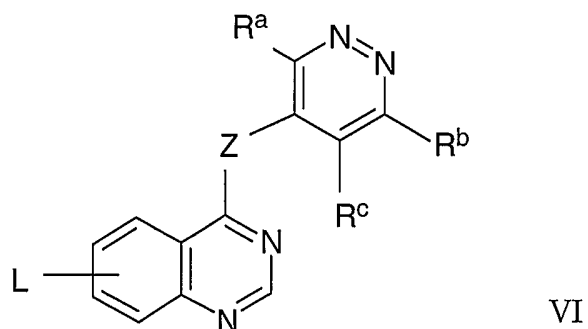
wherein Q^1 is an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group or an optionally substituted alkyl group and X^1 is an oxygen atom, the coupling of a quinazoline of the Formula V



5

wherein m , R^1 , Z , R^a , R^b and R^c 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 conventional means;

- 10 (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



- 15 wherein L is a displaceable group and Z , R^a , R^b and R^c 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 R^1 is a halogeno-substituted (1-6C)alkoxy group with a nitrogen-containing heterocyclyl compound or an appropriate amine;
- 20

- (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 R¹ 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 SO₂ 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 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 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/GB2004/002365

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/12 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.
X	WO 01/21597 A (ASTRAZENECA UK LTD ; KEEN NICHOLAS JOHN (GB); MORTLOCK ANDREW AUSTEN) () 29 March 2001 (2001-03-29) page 3, line 9 - line 12; claim 1 -----	1-10
X	US 5 721 237 A (MYERS MICHAEL R ET AL) 24 February 1998 (1998-02-24) column 2, line 9 - line 56; claim 1 -----	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

24 August 2004

Date of mailing of the international search report

01/09/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Johnson, C

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB2004/002365

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0121597	A	29-03-2001	AU 762697 B2	03-07-2003
			AU 7301900 A	24-04-2001
			BG 106526 A	31-10-2002
			BR 0014137 A	21-05-2002
			CA 2384296 A1	29-03-2001
			CN 1391563 T	15-01-2003
			CZ 20021008 A3	12-06-2002
			EE 200200118 A	15-04-2003
			EP 1218355 A1	03-07-2002
			WO 0121597 A1	29-03-2001
			HU 0300205 A2	28-05-2003
			JP 2003509500 T	11-03-2003
			NO 20021400 A	06-05-2002
			PL 354870 A1	08-03-2004
			SK 3872002 A3	03-12-2002
			TR 200200717 T2	21-06-2002
			ZA 200202232 A	19-06-2003
US 5721237	A	24-02-1998	US 5480883 A	02-01-1996
			AU 696456 B2	10-09-1998
			AU 6104496 A	24-12-1996
			BR 9608638 A	29-06-1999
			CA 2223016 A1	12-12-1996
			CN 1187129 A ,B	08-07-1998
			CZ 9703503 A3	18-03-1998
			EA 840 B1	24-04-2000
			EP 0831831 A1	01-04-1998
			HU 9802702 A2	29-03-1999
			JP 11507355 T	29-06-1999
			SI 9620092 A	31-08-1998
			SK 166397 A3	03-06-1998
			WO 9639145 A1	12-12-1996
			AU 1305095 A	27-06-1995
			EP 0871448 A1	21-10-1998
			SG 54172 A1	16-11-1998
			WO 9515758 A1	15-06-1995
			US 5710158 A	20-01-1998
			US 5795889 A	18-08-1998
			US 5646153 A	08-07-1997
			US RE37650 E1	09-04-2002
			US 6645969 B1	11-11-2003
			US 2004014774 A1	22-01-2004
			US 5714493 A	03-02-1998
			US 6057320 A	02-05-2000
			US RE36256 E	20-07-1999
			AT 159009 T	15-10-1997
			AU 658646 B2	27-04-1995
			AU 1993492 A	30-12-1992
			CA 2102780 A1	11-11-1992
			DE 69222637 D1	13-11-1997
			DE 69222637 T2	26-02-1998
			DK 584222 T3	23-02-1998
			EP 0584222 A1	02-03-1994
			ES 2108120 T3	16-12-1997
			GR 3024955 T3	30-01-1998
			JP 3507071 B2	15-03-2004
			JP 6507643 T	01-09-1994
			MX 9202181 A1	01-05-1993

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB2004/002365

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5721237	A	SG 64322 A1	27-04-1999
		WO 9220642 A1	26-11-1992
		US 5409930 A	25-04-1995