SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21. **EXPEDIENTE No.** 05-42313

54. **TITULO** DERIVADOS DE QUINAZOLINA COMO INHIBIDORES DE SRC TIROSINA CINASA

51. **CLASIFICACION INTERNACIONAL** A61K31/517; A61P35/00

71. **SOLICITANTE** ASTRAZENECA AB

DOMICILIO SODERTALJE. SUECIA

74. **APODERADO** JUAN PABLO CADENA SARMIENTO

22. **SANTAFE DE BOGOTA, D.C.** 03/05/2005

P

(FORMA P 10)

Oficina de Comunicaciones

+1

PETITORIO

AS: 96.866

Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05042313 00038830 Folios: 231
Fecha (AMD): 2005-05-03 16:59:02
Tramite : 011 PCT-PATENT 379 FASE NACI 421 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL 06-06-05

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capítulo I ☒ Capítulo II.

2 SOLICITANTE (71)	Nombre: **ASTRAZENECA AB** Dirección: S-1-51 85 Sodertalje, Suecia Nacionalidad o Domicilio Suecia Lugar de Constitución Suecia Teléfono: Fax: E-mail	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número
3 REPRESENTANTE O APODERADO	Nombre: **JUAN PABLO CADENA SARMIENTO** Dirección: Cra. 7 No 16-56 Piso 9 Teléfono 380-2200 Fax: 380-2700 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número 80.410.337 TP 57492
4 INVENTOR (ES) (72)	Nombre. Patrick Ple Dirección: AstraZeneca Pharma, Z.I. La Pompelle, BP 1050, F-51689 Reims Cedex 2, Francia Nacionalidad o Domicilio: Francia	

5 PCT (86)
Solicitud Internacional No. PCT/GB2003/004703 Fecha 29-10-2003
Publicación Internacional No. WO 2004/041829 A1 Fecha 21-05-2004

Título (54): DERIVADOS DE QUINAZOLINA COMO INHIBIDORES DE SRC TIROSINA CINASA

7 Clasificación Internacional (51) A61K31/517 · A61P35/00

8 Prioridad SI ☒ NO ☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	EP	04-11-2002	02292736.2
	EP	10-04-2003	03290900.4

9 Comprobante de pago No. 05-26.034 **Fecha** 03-05-2005

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

10 ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud $443.000
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [x] Poderes, si fuere el caso **Fotocopia Autenticada**
- [x] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [x] Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA
- [ ] Traducción del examen preliminar efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [ ] Arte final 12x12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [x] Otros Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente.

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA:

C.C. 80.410.337 de Usaquén T.P. 57492 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05842313 00000000
Fecha (AMD) 2005-05-03 16:59:02 Folios: 231
Tramite : 811 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 05 - 26,034
FECHA : ABRIL 11 DE 2005

C O N S I G N A C I O N

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	36794009	11/04/2005	33,070,000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	443,000.00
		TOTAL : $	443,000.00

SON: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

PATENTE [X] PCT/GB2003/004703 MODELO DE UTILIDAD [ ] DISEÑO INDUSTRIAL [ ]

SOLICITANTE/S RAZON SOCIAL O APELLIDOS Y NOMBRES ASTRAZENECA AB

DOMICILIO SODERTALJE, SUECIA
APODERADO JUAN PABLO CADENA SARMIENTO
TITULO DERIVADOS DE QUINAZOLINA COMO INHIBIDORES DE SRC TIROSINA CINASA

CLASIFICACION
EXPEDIENTE No FECHA DE SOLICITUD ROLLO MICROFILM
CERTIFICADO No FECHA DE CONCESION VIGENCIA DESDE HASTA
PRORROGA CAMBIO DE NOMBRE
TRASPASO A
INVENTOR (ES) PATRICK PLE
OTROS

OFICINA DE COMUNICACIONES

76.866

5

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 May 2004 (21.05.2004).

PCT

(10) International Publication Number
WO 2004/041829 A1

(51) International Patent Classification[7]: C07D 491/04, 519/00, A61K 31/517, A61P 35/00

(21) International Application Number: PCT/GB2003/004703

(22) International Filing Date: 29 October 2003 (29 10.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02292736.2 4 November 2002 (04 11 2002) EP
03290900 4 10 April 2003 (10 04 2003) EP

(71) Applicant *(for AE, AG, AL, AM, AT, AU, AZ, BA, BB, BE, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, FR, GB, GD, GE, GH, GM, GR, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, SZ, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW only)*: ASTRAZENECA AB [SE/SE], Sodertalje, S-151 85 (SE).

(71) Applicant *(for MG only)*: ASTRAZENECA UK LIMITED [GB/GB], 15 Stanhope Gate, London, Greater London W1K 1LN (GB)

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: PLE, Patrick [FR/FR], AstraZeneca Pharma, Z I. La Pompelle, BP 1050, F-51689 Reims Cedex 2 (FR)

(74) Agent: TAIT, Brian, Steele, ASTRAZENECA, Global Intellectual Property, P O Box 272, Mereside, Macclesfield, Cheshire SK10 4GR (GB)

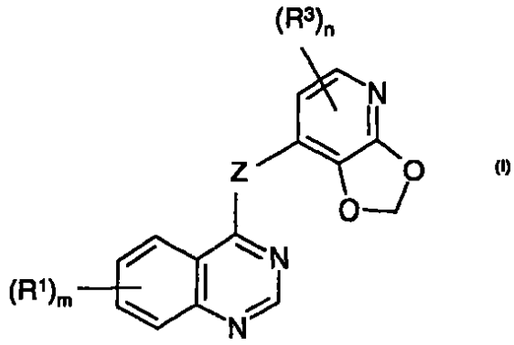
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, 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 *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (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 "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette

(54) Title: QUINAZOLINE DERIVATIVES AS SRC TYROSINE KINASE INHIBITORS



(I)

(57) Abstract: The invention concerns quinazoline derivatives of Formula (I) (A chemical formula should be inserted here - please see paper copy enclosed herewith) wherein Z is an O, S, SO, SO_2, $N(R^2)$ or $C(R^2)_2$ group wherein each R^2 group is hydrogen or (1-8C) alkyl m is 0, 1, 2 or 3, each R^1 group is selected from halogeno, (1-8C) alkyl, (1-6C) alkoxy and any of the other meanings defined in the description, n is 0, 1, 2 or 3, and each R^3 group is selected from halogeno, (1-8C) alkyl, (1-6C) alkoxy and any of the other meanings defined in the description, or pharmaceutically-acceptable salts 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

WO 2004/041829 A1

QUINAZOLINE DERIVATIVES AS SRC TYROSINE KINASE INHIBITORS

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 $pp60^{v\text{-}Src}$ tyrosine kinase (otherwise known as v-Src), and the corresponding tyrosine kinases in normal cells, for example $pp60^{c\text{-}Src}$ tyrosine kinase (otherwise known as c-Src)

Receptor tyrosine kinases are important in the transmission of biochemical signals which initiate 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, TGFα, Neu and erbB receptors, Class II receptor tyrosine kinases comprising the insulin family of receptor tyrosine kinases such as the insulin and IGF1 receptors and insulin-related receptor (IRR) and Class III receptor tyrosine kinases comprising the platelet-derived growth factor (PDGF) family of receptor tyrosine kinases such as the PDGFα, PDGFβ and colony-stimulating factor 1 (CSF1) receptors.

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

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

(Lutz *et 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 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 (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 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 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. It is advantageous to minimise VEGF receptor tyrosine kinase inhibitory activity as some compounds having that activity have been found to act as potassium channel blockers, for example in a human ether-a-go-go-related-gene (hERG)-encoded potassium channel assay. Such activity may give rise to electrocardiogram (ECG) changes in vivo.

The anti-cancer treatment defined hereinafter 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. It is well known that nearly all drugs are metabolised to some degree in the human, generally to a less lipid soluble compound which is more easily excreted

by the kidney. Many of the drug metabolic enzymes are found in the endoplasmic reticulum (which form microsomes upon homogenisation) of hepatocytes. The liver is the major site of drug metabolism because the liver cells (hepatocytes) contain particularly high concentrations of drug metabolising enzymes. Cytochrome P450 is a family of isoenzymes found in hepatic microsomes. Six specific P450 isoenzymes are responsible for the metabolism of most of the commonly used drugs, namely P450 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. Combination chemotherapy can be problematic if one or more of the component drugs of the combination are metabolised by Cytochtome P450 3A4 (hereinafter CYP 3A4). Such a component may be a substrate for CYP 3A4 or it may be an inducer or an inhibitor of that isoenzyme. Such effects can affect the pharmacokinetics of the other component of the combination therapy.

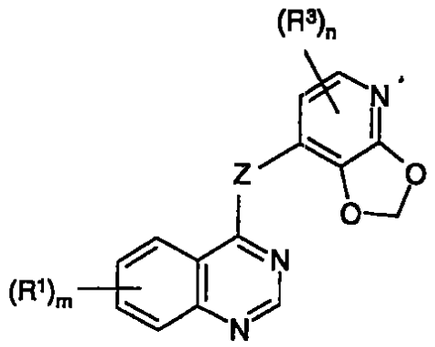
We have established that certain compounds of the present invention have the advantageous property of being less liable to metabolism by such P450 isoenzymes, particularly by CYP 3A4. Accordingly, it is possible to administer such compounds in combination anti-cancer therapy with greater safety.

We have further established that certain compounds of the present invention are doubly advantageous in that they possess little activity against VEGF receptor tyrosine kinase and they show little or no tendency to be metabolised by P450 isoenzymes such as CYP 3A4.

It is stated in International Patent Application WO 01/94341 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 5-substituted quinazoline derivatives including certain 5-substituted 4-(2,3-methylenedioxyanilino)quinazolines. There is no disclosure therein of any 4-(2,3-methylenedioxypyrid-4-ylamino)quinazoline derivatives.

It is stated in International Patent Application WO 02/16352 that a range of 4-(2,3-methylenedioxyanilino)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 no disclosure therein of any 4-(2,3-methylenedioxypyrid-4-ylamino)quinazoline derivatives.

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



I

wherein **Z** is an O, S, SO, SO_2, $N(R^2)$ or $C(R^2)_2$ group wherein each R^2 group, which may be the same or different, is hydrogen or (1-8C)alkyl;

m is 0, 1, 2 or 3;

each R^1 group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, (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 :

$$Q^1\text{-}X^1\text{-}$$

wherein X^1 is a direct bond or is selected from O, S, SO, SO_2, $N(R^4)$, CO, $CH(OR^4)$, $CON(R^4)$, $N(R^4)CO$, $SO_2N(R^4)$, $N(R^4)SO_2$, $OC(R^4)_2$, $SC(R^4)_2$ and $N(R^4)C(R^4)_2$, wherein R^4 is hydrogen or (1-8C)alkyl, and Q^1 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)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 R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO_2, $N(R^5)$, CO, $CH(OR^5)$, $CON(R^5)$, $N(R^5)CO$, $SO_2N(R^5)$, $N(R^5)SO_2$, CH=CH and C≡C wherein R^5 is hydrogen or (1-8C)alkyl or, when the inserted group is $N(R^5)$, R^5 may also be (2-6C)alkanoyl,

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= 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 :

$$Q^2-X^2-$$

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

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-8C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, oxo, thioxo, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^3-Q^3$$

wherein X^3 is a direct bond or is selected from O, S, SO, SO_2, $N(R^7)$, CO, $CH(OR^7)$, $CON(R^7)$, $N(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, $C(R^7)_2O$, $C(R^7)_2S$ and $N(R^7)C(R^7)_2$, wherein R^7 is hydrogen or (1-8C)alkyl, and Q^3 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

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

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

$$-X^4-R^8$$

wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-8C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, or from a group of the formula :

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

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

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

n is 0, 1, 2 or 3; and

each R^3 group, which may be the same or different, is 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, (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 :

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

wherein X^6 is a direct bond or is selected from O and $N(R^{12})$, wherein R^{12} is hydrogen or (1-8C)alkyl, and R^{11} is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl or di-[(1-6C)alkyl]amino-(1-6C)alkyl, or from a group of the formula :

$$-X^7-Q^5$$

wherein X^7 is a direct bond or is selected from O, S, SO, SO_2, $N(R^{13})$, CO, $CH(OR^{13})$, $CON(R^{13})$, $N(R^{13})CO$, $SO_2N(R^{13})$, $N(R^{13})SO_2$, $C(R^{13})_2O$, $C(R^{13})_2S$ and $N(R^{13})C(R^{13})_2$, wherein R^{13} is hydrogen or (1-8C)alkyl, and Q^5 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy, and any heterocyclyl group within Q^5 optionally bears 1 or 2 oxo or thioxo substituents;

or a pharmaceutically-acceptable salt thereof.

According to a further aspect of the invention there is provided a quinazoline derivative of the Formula I as defined hereinbefore

wherein **Z** is O, S, SO, SO_2, CH_2 or NH;

m is 0, 1, 2 or 3;

each R^1 group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, (1-6C)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 :

$$Q^1\text{-}X^1\text{-}$$

wherein X^1 is a direct bond or is selected from O, S, SO, SO_2, $N(R^4)$, CO, $CH(OR^4)$, $CON(R^4)$, $N(R^4)CO$, $SO_2N(R^4)$, $N(R^4)SO_2$, $OC(R^4)_2$, $SC(R^4)_2$ and $N(R^4)C(R^4)_2$, wherein R^4 is hydrogen or (1-6C)alkyl, and Q^1 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)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 R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO_2, $N(R^5)$, CO, $CH(OR^5)$, $CON(R^5)$, $N(R^5)CO$, $SO_2N(R^5)$, $N(R^5)SO_2$, CH=CH and C≡C wherein

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

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= 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

$$Q^2-X^2-$$

wherein X^2 is a direct bond or is selected from CO and $N(R^6)CO$, wherein R^6 is hydrogen or (1-6C)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 (1-6C)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 :

$$-X^3-Q^3$$

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

$$-X^4-R^8$$

wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, or from a group of the formula :

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

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

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

n is 0, 1, 2 or 3; and

each R^3 group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, nitro, hydroxy, amino, carboxy, carbamoyl, (1-6C)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 :

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

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

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

$$-X^7-Q^5$$

wherein X^7 is a direct bond or is selected from O, S, SO, SO_2, $N(R^{13})$, CO, $CH(OR^{13})$, $CON(R^{13})$, $N(R^{13})CO$, $SO_2N(R^{13})$, $N(R^{13})SO_2$, $C(R^{13})_2O$, $C(R^{13})_2S$ and $N(R^{13})C(R^{13})_2$, wherein R^{13} is hydrogen or (1-6C)alkyl, and Q^5 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different, selected from halogeno, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy, and any heterocyclyl group within Q^5 optionally bears 1 or 2 oxo or thioxo substituents;

or a pharmaceutically-acceptable salt thereof.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and tert-butyl, and also (3-7C)cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and also (3-7C)cycloalkyl-(1-2C)alkyl groups such as cyclopropylmethyl, 2-cyclopropylethyl, cyclobutylmethyl, 2-cyclobutylethyl, cyclopentylmethyl, 2-cyclopentylethyl, cyclohexylmethyl and 2-cyclohexylethyl. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only, references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only and references to individual cycloalkyl groups such as "cyclopentyl" are specific for that 5-membered ring only. An analogous convention applies to other generic terms, for example (1-6C)alkoxy includes (3-6C)cycloalkyloxy groups and (3-5C)cycloalkyl-(1-2C)alkoxy groups, for example methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cyclopropylmethoxy, 2-cyclopropylethoxy, cyclobutylmethoxy, 2-cyclobutylethoxy and cyclopentylmethoxy; (1-6C)alkylamino includes (3-6C)cycloalkylamino groups and (3-5C)cycloalkyl-(1-2C)alkylamino groups, for example methylamino, ethylamino, propylamino, cyclopropylamino, cyclobutylamino, cyclohexylamino, cyclopropylmethylamino, 2-cyclopropylethylamino, cyclobutylmethylamino, 2-cyclobutylethylamino and cyclopentylmethylamino; and di-[(1-6Calkyl]amino includes di-[(3-6C)cycloalkyl]amino groups and di-[(3-5C)cycloalkyl-(1-2C)alkyl]amino groups, for example dimethylamino, diethylamino, dipropylamino, N-cyclopropyl-N-methylamino, N-cyclobutyl-N-methylamino, N-cyclohexyl-N-ethylamino, N-cyclopropylmethyl-

N-methylamino, N-(2-cyclopropylethyl)-N-methylamino and N-cyclopentylmethyl-N-methylamino.

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

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

A suitable value for any one of the 'Q' groups (Q^1 to Q^5) 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 (3-7C)cycloalkyl or for the (3-7C)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 (3-7C)cycloalkenyl or for the (3-7C)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^5) 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^5) when it is heterocyclyl or for the heterocyclyl group within a 'Q' group is, for example, a non-aromatic saturated or partially saturated 3 to 10 membered monocyclic or bicyclic ring with up to five heteroatoms selected from oxygen, nitrogen and sulphur, for example oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, oxepanyl, tetrahydrothienyl, 1,1-dioxotetrahydrothienyl, tetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, azetidinyl, 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, 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, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group is present.

It is to be understood that there is a hydrogen atom at the 2-position on the quinazoline ring in structural Formula I. Thereby the R^1 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. It is further to be understood that the R^3 group that may be present on the 2,3-methylenedioxypyridyl group within structural Formula I may be located on either the 5- or 6-membered ring portions thereof, *i.e.* an R^3 group may be located on the pyridyl ring or on the methylene group within the 2,3-methylenedioxypyridyl group. For example, the R^3 group may be a methyl group that is located on the methylene group portion of the 2,3-methylenedioxypyridyl group *i.e.* the 2- and 3-positions on the pyridyl group bear an ethylidenedioxy group. Preferably, any R^3 group that is present on the 2,3-methylenedioxypyridyl group within structural Formula I is located on the pyridyl ring thereof. It is further to be understood that, when multiple R^3 groups are present, the R^3 groups may be the same or different.

Suitable values for any of the 'R' groups (R^1 to R^{13}) or for various groups within an R^1 or R^3 substituent include -

for halogeno	fluoro, chloro, bromo and iodo;
for (1-8C)alkyl:	methyl, ethyl, propyl, isopropyl, tert-butyl, cyclobutyl, cyclopentyl and 2-cyclopropylethyl;
for (1-6C)alkyl:	methyl, ethyl, propyl, isopropyl and tert-butyl;
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: vinyloxy and allyloxy;

for (2-6C)alkynyloxy: ethynyloxy and 2-propynyloxy;

for (1-6C)alkylthio: methylthio, ethylthio and propylthio;

for (1-6C)alkylsulphinyl: methylsulphinyl and ethylsulphinyl;

for (1-6C)alkylsulphonyl: methylsulphonyl and ethylsulphonyl;

for (1-6C)alkylamino: methylamino, ethylamino, propylamino, isopropylamino and butylamino;

for di-[(1-6C)alkyl]amino: dimethylamino, diethylamino, N-ethyl-N-methylamino and diisopropylamino;

for (1-6C)alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;

for N-(1-6C)alkylcarbamoyl: N-methylcarbamoyl, N-ethylcarbamoyl and N-propylcarbamoyl;

for N,N-di-[(1-6C)alkyl]carbamoyl: N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl;

for (2-6C)alkanoyl: acetyl, propionyl and isobutyryl;

for (2-6C)alkanoyloxy: acetoxy and propionyloxy;

for (2-6C)alkanoylamino: acetamido and propionamido;

for N-(1-6C)alkyl-(2-6C)alkanoylamino: N-methylacetamido and N-methylpropionamido;

for N-(1-6C)alkylsulphamoyl: N-methylsulphamoyl and N-ethylsulphamoyl;

for N,N-di-[(1-6C)alkyl]sulphamoyl: N,N-dimethylsulphamoyl;

for (1-6C)alkanesulphonylamino: methanesulphonylamino and ethanesulphonylamino;

for N-(1-6C)alkyl-(1-6C)alkanesulphonylamino: N-methylmethanesulphonylamino and N-methylethanesulphonylamino;

for (3-6C)alkenoylamino: acrylamido, methacrylamido and crotonamido;

for N-(1-6C)alkyl-(3-6C)alkenoylamino: N-methylacrylamido and N-methylcrotonamido;

for (3-6C)alkynoylamino: propiolamido;

for N-(1-6C)alkyl-(3-6C)alkynoylamino: N-methylpropiolamido;

for amino-(1-6C)alkyl: aminomethyl, 2-aminoethyl, 1-aminoethyl and 3-aminopropyl;

for (1-6C)alkylamino-(1-6C)alkyl: methylaminomethyl, ethylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl,

2-ethylaminoethyl and 3-methylaminopropyl;

for di-[(1-6C)alkyl]amino-(1-6C)alkyl: dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl and 3-dimethylaminopropyl;

for halogeno-(1-6C)alkyl: chloromethyl, 2-fluoroethyl, 2-chloroethyl, 1-chloroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 3-fluoropropyl, 3-chloropropyl, 3,3-difluoropropyl and 3,3,3-trifluoropropyl;

for hydroxy-(1-6C)alkyl: hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and 3-hydroxypropyl;

for (1-6C)alkoxy-(1-6C)alkyl: methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;

for cyano-(1-6C)alkyl cyanomethyl, 2-cyanoethyl, 1-cyanoethyl and 3-cyanopropyl;

for (2-6C)alkanoylamino-(1-6C)alkyl: acetamidomethyl, propionamidomethyl and 2-acetamidoethyl; and

for (1-6C)alkoxycarbonylamino-(1-6C)alkyl: methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl, tert-butoxycarbonylaminomethyl and 2-methoxycarbonylaminoethyl.

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

When, as defined hereinbefore, an R^1 group forms a group of the formula Q^1-X^1- and, for example, X^1 is a $OC(R^4)_2$ linking group, it is the carbon atom, not the oxygen atom, of the $OC(R^4)_2$ linking group which is attached to the quinazoline ring and the oxygen atom is attached to the Q^1 group. Similarly, when, for example a CH_3 group within a R^1 substituent bears a group of the formula -X^3-Q^3 and, for example, X^3 is a $C(R^7)_2O$ linking group, it is the carbon atom, not the oxygen atom, of the $C(R^7)_2O$ linking group which is attached to the CH_3 group and the oxygen atom is linked to the Q^3 group. A similar convention applies to the attachment of the groups of the formulae Q^2-X^2- and -X^7-Q^5.

As defined hereinbefore, adjacent carbon atoms in any (2-6C)alkylene chain within a R^1 substituent may be optionally separated by the insertion into the chain of a group such as O, CON(R^5) or C≡C. For example, insertion of a C≡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.

When, as defined hereinbefore, any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent such as a group of the formula Q^2-X^2- wherein X^2 is, for example, NHCO and Q^2 is a heterocyclyl-(1-6C)alkyl group, suitable R^1 substituents so formed include, for example, N-[heterocyclyl-(1-6C)alkyl]carbamoylvinyl groups such as N-(2-pyrrolidin-1-ylethyl)carbamoylvinyl or N-[heterocyclyl-(1-6C)alkyl]carbamoylethynyl groups such as N-(2-pyrrolidin-1-ylethyl)carbamoylethynyl.

When, as defined hereinbefore, any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-6C)alkyl substituents, there are suitably 1 or 2 halogeno or (1-6C)alkyl substituents present on each said CH_2 group and there are suitably 1, 2 or 3 such substituents present on each said CH_3 group.

When, as defined hereinbefore, any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group a substituent as defined hereinbefore, suitable R^1 substituents so formed include, for example, hydroxy-substituted heterocyclyl-(1-6C)alkoxy groups such as 2-hydroxy-3-piperidinopropoxy and 2-hydroxy-3-morpholinopropoxy, hydroxy-substituted amino-(2-6C)alkoxy groups such as 3-amino-2-hydroxypropoxy, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkoxy groups such as 2-hydroxy-3-methylaminopropoxy, hydroxy-substituted di-[(1-6C)alkyl]amino-(2-6C)alkoxy groups such as 3-dimethylamino-2-hydroxypropoxy, hydroxy-substituted heterocyclyl-(1-6C)alkylamino groups such as 2-hydroxy-3-piperidinopropylamino and 2-hydroxy-3-morpholinopropylamino, hydroxy-substituted amino-(2-6C)alkylamino groups such as 3-amino-2-hydroxypropylamino, hydroxy-substituted (1-6C)alkylamino-(2-6C)alkylamino groups such as 2-hydroxy-3-methylaminopropylamino, hydroxy-substituted di-[(1-6C)alkyl]amino-(2-6C)alkylamino groups such as 3-dimethylamino-2-hydroxypropylamino, hydroxy-substituted (1-6C)alkoxy groups such as 2-hydroxyethoxy, (1-6C)alkoxy-substituted (1-6C)alkoxy groups such as 2-methoxyethoxy and

3-ethoxypropoxy, (1-6C)alkylsulphonyl-substituted (1-6C)alkoxy groups such as 2-methylsulphonylethoxy and heterocyclyl-substituted (1-6C)alkylamino-(1-6C)alkyl groups such as 2-morpholinoethylaminomethyl, 2-piperazin-1-ylethylaminomethyl and 3-morpholinopropylaminomethyl.

It is to be understood that when, as defined hereinbefore, any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group a substituent as defined hereinbefore, such an optional substituent may be present on a CH_2 or CH_3 group within the hereinbefore defined substituents that may be present on an aryl, heteroaryl or heterocyclyl group within a R^1 substituent. For example, if R^1 includes an aryl or heteroaryl group that is substituted by a (1-8C)alkyl group, the (1-8C)alkyl group may be optionally substituted on a CH_2 or CH_3 group therein by one of the hereinbefore defined substituents therefor. For example, if R^1 includes a heteroaryl group that is substituted by, for example, a (1-6C)alkylamino-(1-6C)alkyl group, the terminal CH_3 group of the (1-6C)alkylamino group may be further substituted by, for example, a (1-6C)alkylsulphonyl group or a (2-6C)alkanoyl group. For example, the R^1 group may be a heteroaryl group such as a thienyl group that is substituted by a N-(2-methylsulphonylethyl)aminomethyl group such that R^1 is, for example, a 5-[N-(2-methylsulphonylethyl)aminomethyl]thien-2-yl group. Further, for example, if R^1 includes a heterocyclyl group such as a piperidinyl or piperazinyl group that is substituted on a nitrogen atom thereof by, for example, a (2-6C)alkanoyl group, the terminal CH_3 group of the (2-6C)alkanoyl group may be further substituted by, for example, a di-[(1-6C)alkyl]amino group. For example, the R^1 group may be a N-(2-dimethylaminoacetyl)piperidin-4-yl group or a 4-(2-dimethylaminoacetyl)piperazin-1-yl group.

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

Particular novel compounds of the invention include, for example, quinazoline derivatives of the Formula I, or pharmaceutically-acceptable salts thereof, wherein, unless

otherwise stated, each of Z, m, R^1, n and R^3 has any of the meanings defined hereinbefore or in paragraphs (a) to (o) hereinafter :-

(a) Z is O, S, SO, SO_2, CH_2 or NH;

(b) Z is O;

(c) Z is NH;

(d) m is 1 or 2, and each R^1 group, which may be the same or different, is selected from halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)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 :

$$Q^1-X^1-$$

wherein X^1 is a direct bond or is selected from O, $N(R^4)$, $CON(R^4)$, $N(R^4)CO$ and $OC(R^4)_2$, wherein R^4 is hydrogen or (1-6C)alkyl, and Q^1 is aryl, aryl-(1-6C)alkyl, 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≡C wherein R^5 is hydrogen or (1-6C)alkyl, or, when the inserted group is $N(R^5)$, R^5 may also be (2-6C)alkanoyl,

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= or HC≡ 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 formula :

$$Q^2-X^2-$$

wherein X^2 is a direct bond or is CO or $N(R^6)CO$, wherein R^6 is hydrogen or (1-6C)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 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 :

$$-X^3-Q^3$$

wherein X^3 is a direct bond or is selected from O, $N(R^6)$, $CON(R^7)$, $N(R^7)CO$ and $C(R^7)_2O$, wherein R^7 is hydrogen or (1-6C)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 halogeno, trifluoromethyl, hydroxy, amino, carbamoyl, (1-6C)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 :

$$-X^4-R^8$$

wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-6C)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 :

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

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

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

Q^1-X^1-

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

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, NH, N(Me), CONH, NHCO, CH=CH and C≡C,

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= 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 the formula :

Q^2-X^2-

wherein X^2 is a direct bond or is CO, NHCO or N(Me)CO and Q^2 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, 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 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 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 :

$$-X^3-Q^3$$

wherein X^3 is a direct bond or is selected from O, NH, CONH, NHCO and CH_2O and Q^3 is pyridyl, pyridylmethyl, pyrrolidin-1-yl, pyrrolidin-2-yl, morpholino, piperidino, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, 2-pyrrolidin-1-ylethyl, 3-pyrrolidin-1-ylpropyl, pyrrolidin-2-ylmethyl, 2-pyrrolidin-2-ylethyl, 3-pyrrolidin-2-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, piperidin-3-ylmethyl, 2-piperidin-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, methoxy, methylsulphonyl, N-methylcarbamoyl, N,N-dimethylcarbamoyl, acetyl, propionyl, isobutyryl, methylenedioxy, ethylidendioxy and isopropylidenedioxy, or optionally bears 1 substituent selected from a group of the formula :

$$-X^4-R^8$$

wherein X^4 is a direct bond or is selected from O and NH and R^8 is 2-fluoroethyl, 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, methoxycarbonylaminomethyl, ethoxycarbonylaminomethyl or tert-butoxycarbonylaminomethyl, and from a group of the formula :

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

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, 2-morpholinoethyl, 3-morpholinopropyl, piperidinomethyl, 2-piperidinoethyl, 3-piperidinopropyl, piperazin-1-ylmethyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, each of which optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

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

(f) m is 1 and the R^1 group is located at the 5-, 6- or 7-position, or m is 2 and the R^1 groups, which may be the same or different, are located at the 5- and 7-positions or at the 6- and 7-positions and each R^1 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 R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(Me), CH=CH and C≡C,

and when R^1 is a vinyl or ethynyl group, the R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from 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 :

$$Q^2-X^2-$$

wherein X^2 is a direct bond or is NHCO or N(Me)CO and Q^2 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 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 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-N-propylamino, acetoxy, acetamido and N-methylacetamido,

and wherein any phenyl, imidazolyl, triazolyl, pyridyl or heterocyclyl group within a substituent on R^1 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, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R^1 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, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

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

(g) m is 1 and the R^1 group is located at the 7-position or m is 2 and the R^1 groups, which may be the same or different, are located at the 6- and 7-positions and each R^1 is selected from 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-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, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

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, NH, CH=CH and C≡C,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more chloro groups or a substituent selected from hydroxy, oxo, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxy,

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

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

(h) m is 1 and the R^1 group is located at the 5-position or m is 2 and the R^1 groups, which may be the same or different, are located at the 5- and 7-positions and each R^1 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, 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, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy,

2-homopiperazin-1-ylethoxy, 3-homopiperazin-1-ylpropoxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy,

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

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more chloro groups or a substituent selected from hydroxy, oxo, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxy,

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

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

(i) 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-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 3-homopiperazin-1-ylpropoxy,

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

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

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

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

(j) 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, 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, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, 2-piperidin-3-ylethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more chloro groups or a substituent selected from hydroxy, oxo, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxy,

and wherein any heterocyclyl group within a substituent on R^1 optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, trifluoromethyl, hydroxy, amino, methyl, ethyl, methoxy, methylenedioxy, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl,

piperazin-1-yl or homopiperazin-1-yl group within a R^1 substituent is optionally N-substituted with methyl, ethyl, propyl, allyl, 2-propynyl, methylsulphonyl, acetyl, propionyl, isobutyryl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl or cyanomethyl,

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

(k) n is 0;

(l) n is 1 or 2 and the R^3 groups, which may be the same or different, are located at the 5- and/or 6-positions of the 2,3-methylenedioxypyridin-4-yl group and are selected from halogeno, trifluoromethyl, cyano, hydroxy, (1-6C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy;

(m) n is 1 or 2 and the R^3 groups, which may be the same or different, are located at the 5- and/or 6-positions of the 2,3-methylenedioxypyridin-4-yl group and are selected from fluoro, chloro, bromo, iodo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, vinyl, allyl, isopropenyl, ethynyl, 1-propynyl, 2-propynyl, methoxy and ethoxy;

(n) n is 0 or n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxypyridin-4-yl group, especially the 5-position, and is selected from fluoro, chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, methoxy and ethoxy; and

(o) n is 1 and the R^3 group is located at the 5-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from fluoro, chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, methoxy and ethoxy.

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, n and R^3 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 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.

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

Z is O or NH;

m is 1 and the R^1 group is located at the 5-, 6- or 7-position or m is 2 and the R^1 groups, which may be the same or different, are located at the 5- and 7-positions or at the 6-

and 7-positions and each R^1 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 R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(Me), CH=CH and C≡C,

and when R^1 is a vinyl or ethynyl group, the R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from 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 :

$$Q^2-X^2-$$

wherein X^2 is a direct bond or is NHCO or N(Me)CO and Q^2 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 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 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-N-propylamino, acetoxy, acetamido and N-methylacetamido,

and wherein any phenyl, imidazolyl, triazolyl, pyridyl or heterocyclyl group within a substituent on R^1 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, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R^1 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, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

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

n is 0 or n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from fluoro, chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, methoxy and ethoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

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

Z is NH;

m is 2 and the 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-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 3-homopiperazin-1-ylpropoxy,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more chloro groups or a substituent selected from hydroxy, oxo, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxy,

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

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

n is 0 or n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, methoxy and ethoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

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

Z is NH;

m is 2 and the first R^1 group is a 6-methoxy group and the second R^1 group is located at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy, 3-[(3RS,4SR)-3,4-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, 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, 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, 3-methylsulphonylpropoxy, 2-(2-methoxyethoxy)ethoxy, 2-(4-pyridyloxy)ethoxy, 3-pyridylmethoxy and 2-cyanopyrid-4-ylmethoxy: and

n is 0 or n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from fluoro, chloro, bromo, trifluoromethyl and cyano;

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 the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy, 3-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]propoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-(4-allylpiperazin-1-yl)ethoxy, 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

n is 1 and the R^3 group is located at the 6-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from chloro and bromo;

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

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more chloro groups or a substituent selected from hydroxy, oxo, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxy,

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

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

n is 0 or n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from fluoro, chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, methoxy and ethoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

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

Z is NH;

m is 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, 1,1-dioxotetrahydrothiopyran-4-yloxy, N-methylazetidin-3-yloxy, N-ethylazetidin-3-yloxy, N-isopropylazetidin-3-yloxy, pyrrolidin-3-yloxy, N-methylpyrrolidin-3-yloxy, pyrrolidin-2-ylmethoxy, 3-piperidinyloxy, N-methylpiperidin-3-yloxy, 4-piperidinyloxy, N-methylpiperidin-4-yloxy, N-allylpiperidin-4-yloxy, N-prop-2-ynylpiperidin-4-yloxy, N-acetylpiperidin-4-yloxy, N-methylsulphonylpiperidin-4-yloxy, 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 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, 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, 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, 3-methylsulphonylpropoxy, 2-(2-methoxyethoxy)ethoxy, 2-(4-pyridyloxy)ethoxy, 3-pyridylmethoxy and 2-cyanopyrid-4-ylmethoxy;

n is 0 or n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, methoxy and ethoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

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

Z is NH;

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

or m is 2 and the first R^1 group is located at the 5-position and is selected from the group of substituents listed immediately above and the second R^1 group is located at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-[(3RS,4SR)-3,4-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, 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, 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, 3-methylsulphonylpropoxy, 2-(2-methoxyethoxy)ethoxy, 2-(4-pyridyloxy)ethoxy, 3-pyridylmethoxy and 2-cyanopyrid-4-ylmethoxy:

n is 0 or n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, methoxy and ethoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

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

Z is NH;

m is 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 group of substituents listed immediately above, and the second R^1 group is located at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy, 3-[(3RS,4SR)-3,4-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, 3-piperidinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 4-piperazin-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 3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy; and

n is 0 or n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from fluoro, chloro, bromo, trifluoromethyl and cyano;

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 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, 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-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 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-hydroxyethyl)piperazin-1-yl]ethoxy, 3-[4-(2-hydroxyethyl)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-(2-dimethylaminoacetyl)piperazin-1-yl]ethoxy and 3-[4-(2-dimethylaminoacetyl)piperazin-1-yl]propoxy; and

n is 1 and the R^3 group is located at the 5-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from chloro and bromo;

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 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,

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, 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

n is 1 and the R^3 group is located at the 5-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from chloro and bromo;

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 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, 2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperidinoethoxy, 2-piperazin-1-ylethoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 2-(4-prop-2-ynylpiperazin-1-yl)ethoxy, 3-(4-prop-2-ynylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy, 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethoxy and 2-[4-(2-dimethylaminoacetyl)piperazin-1-yl]ethoxy; and

n is 1 and the R^3 group is located at the 5-position of the 2,3-methylenedioxypyridin-4-yl group and is a chloro group;

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 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, 2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy, 2-morpholinoethoxy, 2-piperidinoethoxy, 2-piperazin-1-ylethoxy,

2-(4-methylpiperazin-1-yl)ethoxy, 2-(4-prop-2-ynylpiperazin-1-yl)ethoxy, 2-(4-acetylpiperazin-1-yl)ethoxy, 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethoxy and 2-[4-(2-dimethylaminoacetyl)piperazin-1-yl]ethoxy; and

n is 1 and the R^3 group is located at the 5-position of the 2,3-methylenedioxypyridin-4-yl group and is a chloro group;

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 5-isopropoxy group and the second R^1 group is located at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy, 2-morpholinoethoxy, 2-piperidinoethoxy, 2-piperazin-1-ylethoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 2-(4-acetylpiperazin-1-yl)ethoxy and 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethoxy; and

n is 1 and the R^3 group is located at the 5-position of the 2,3-methylenedioxypyridin-4-yl group and is a chloro group;

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 5-isopropoxy group and the second R^1 group is located at the 7-position and is selected from 2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy, 2-piperazin-1-ylethoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 2-(4-acetylpiperazin-1-yl)ethoxy and 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethoxy; and

n is 1 and the R^3 group is located at the 5-position of the 2,3-methylenedioxypyridin-4-yl group and is a chloro group;

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 Example 3, and Example 6(1) to 6(7) hereinafter.

A particular compound of the invention is, for example, a quinazoline derivative of the Formula I selected from :-

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxy-7-[3-(4-prop-2-ynylpiperazin-1-yl)propoxy]quinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-[3-(4-isobutyrylpiperazin-1-yl)propoxy]-6-methoxyquinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxy-7-{3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy}quinazoline and

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxy-7-[2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is, for example, a quinazoline derivative of the Formula I selected from :-

7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy}-5-tetrahydropyran-4-yloxyquinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-[2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-[3-(4-prop-2-ynylpiperazin-1-yl)propoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(2-morpholinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline and

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(3-morpholinopropoxy)-5-tetrahydropyran-4-yloxyquinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

A further particular compound of the invention is, for example, a quinazoline derivative of the Formula I selected from .-

7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxy-7-(2-piperazin-1-ylethoxy)quinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[4-(2-hydroxyethyl)piperazin-1-yl]ethoxy}-5-isopropoxyquinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxy-7-(2-pyrrolidin-1-ylethoxy)quinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxy-7-(2-piperidinoethoxy)quinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxy-7-(2-morpholinoethoxy)quinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxy-7-(3-morpholinopropoxy)quinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxy-7-[2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]quinazoline,

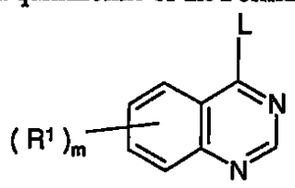
4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxy-7-[2-(4-methylpiperazin-1-yl)ethoxy]quinazoline and

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[4-(2-dimethylaminoacetyl)piperazin-1-yl]ethoxy}-5-isopropoxyquinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

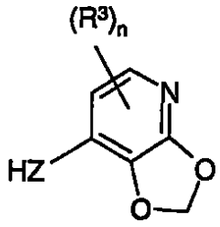
A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a quinazoline derivative of the Formula I are provided as a further feature of the invention and are illustrated by the following representative process variants in which, unless otherwise stated, m, R^1, Z, n and R^3 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 $N(R^2)$ 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 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(R^2) and n, R^3 and R^2 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, whereafter any protecting group that is present is removed by conventional means.

The reaction may conveniently be carried out in the presence of a suitable acid or in the presence of a suitable base. A suitable acid is, for example, an inorganic acid such as, for example, hydrogen chloride or hydrogen bromide. A suitable base is, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4.0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide, 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 out in the presence of a suitable inert solvent or diluent, for example an alcohol or ester such as methanol, ethanol, isopropanol or ethyl acetate, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, for example, 0 to 250°C, preferably in the range 0 to 120°C.

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

The quinazoline derivative of the Formula I may be obtained from this process in the form of the free base or alternatively it may be obtained in the form of a salt with the acid of the formula H-L wherein L has the meaning defined hereinbefore. When it is desired to obtain the free base from the salt, the salt may be treated with a suitable base, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, N-methylmorpholine or diazabicyclo[5.4 0]undec-7-ene, or, for example, an alkali or alkaline earth metal carbonate or hydroxide, for example sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide.

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

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

A carboxy protecting group may be the residue of an ester-forming aliphatic or arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (for example isopropyl, and tert-butyl); lower alkoxy- lower alkyl groups (for example methoxymethyl, ethoxymethyl and isobutoxymethyl); lower acyloxy-lower alkyl groups, (for example 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 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.

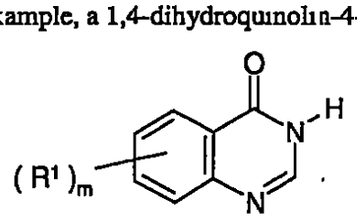
Examples of hydroxy protecting groups include lower alkyl groups (for example tert-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxycarbonyl groups (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl);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

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 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



IV

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

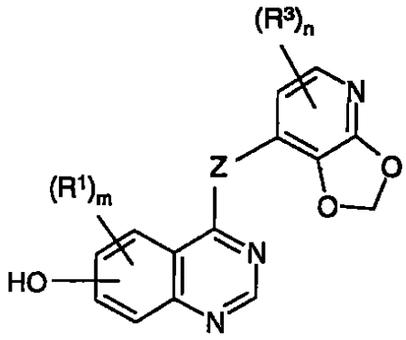
The 4-chloroquinazoline so obtained may be converted, if required, into a 4-pentafluorophenoxyquinazoline by reaction with pentafluorophenol in the presence of a suitable base such as potassium carbonate and in the presence of a suitable solvent such as N,N-dimethylformamide.

4-Amino-2,3-methylenedioxypyridine 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-mercapto-2,3-methylenedioxypyridine 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 group of the formula

$$Q^1\text{-}X^1\text{-}$$

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, conveniently in the presence of a suitable dehydrating agent, of a quinazoline of the Formula V



V

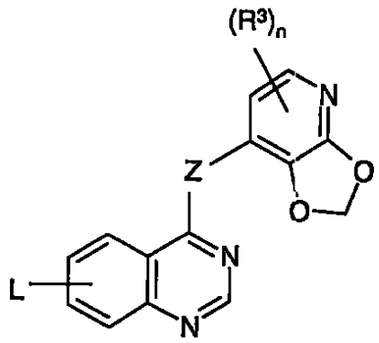
wherein m, R^1, Z, n and R^3 have any of the meanings defined hereinbefore except that any functional group is protected if necessary, with an appropriate alcohol wherein any functional group is protected if necessary whereafter any protecting group that is present is removed by conventional means

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

an azo compound such as diethyl or di-tert-butyl azodicarboxylate and a phosphine such as triphenylphosphine. The reaction is conveniently carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride and at a temperature in the range, for example, 10 to 150°C, preferably at or near ambient temperature.

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

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



VI

wherein L is a displaceable group as defined hereinbefore and Z, n and R^3 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 by conventional means.

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

(d) For the production of those compounds of the Formula I wherein R^1 is an amino-substituted (1-6C)alkoxy group (such as a 2-(4-methylpiperazin-1-yl)ethoxy or 3-dimethylaminopropoxy group), the reaction of a compound of the Formula I wherein R^1 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 carrier as defined hereinbefore and at a temperature in the range 10 to 180°C, preferably in the range 60 to 120°C.

(e) For the production of those compounds of the Formula I wherein R^1 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 the Formula I wherein the R^1 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 SO_2 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.

(g) For the production of those compounds of the Formula I wherein an R^1 group contains an N-acylated heterocyclic group, the acylation, conveniently in the presence of a suitable base as defined hereinbefore, of a quinazoline derivative of the Formula I wherein the R^1 group contains a heterocyclic group having an unsubstituted NH group.

Suitable acylating agents are well known to the man skilled in the art and examples thereof are illustrated in the Examples. For example, a compound of the Formula I wherein a R^1 group contains a piperidinyl or piperazinyl group having an unsubstituted NH group may be reacted under conventional conditions with an optionally substituted carboxylic acid or a reactive derivative thereof.

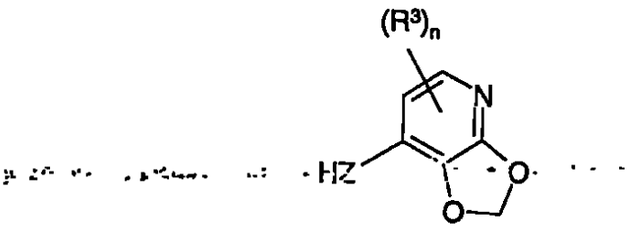
A suitable reactive derivative of an optionally substituted carboxylic acid is, for example, a carboxylic acid halide; a carboxylic acid amide; a mixed anhydride, for example an anhydride formed by the reaction of the carboxylic acid and a chloroformate such as isobutyl chloroformate; the product of the reaction of the carboxylic acid with a carbodiimide such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide; the product of the reaction of the carboxylic acid with a mixture of an azo compound such as diethyl or di-*tert*-butyl azodicarboxylate and a phosphine such as triphenylphosphine, or the product of the reaction of the carboxylic acid with a uronium salt such as 2-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate(V). For example, a suitable amino-

substituted carboxylic acid is N,N-dimethylglycine and a suitable reactive derivative thereof is 2-dimethylaminoacetyl chloride.

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.

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 quinazoline derivative with a suitable acid using a conventional procedure.

Many of the intermediates defined herein are novel and these are provided as a further feature of the invention. For example, many compounds of the Formula III



III

wherein Z is O, S, or N(R^2) and n, R^3 and R^2 have any of the meanings defined hereinbefore are novel compounds. For example, although 4-amino-2,3-methylenedioxypyridine starting materials (Formula III, for example when Z is NH) may be obtained by conventional procedures as illustrated in the Examples, compounds such as 4-amino-5-chloro-2,3-methylenedioxypyridine is a novel compound which is provided as a further feature of the invention.

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, as inhibitors in vivo of the growth in nude mice of xenografts of A549 tissue, and for inhibition in vitro of the hERG-encoded potassium channel.

(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 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 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-culture-treated clear assay plates (Costar) each containing an assay medium comprising Dulbecco's modified Eagle's medium (DMEM; Sigma) plus 0.5% foetal calf serum (FCS), 2mM glutamine, 100 units/ml penicillin and 0.1mg/ml streptomycin in 0.9% aqueous sodium chloride solution. The plates were incubated overnight at 37°C in a humidified (7.5% CO_2 : 95% air) incubator.

Test compounds were solubilised in DMSO to form a 10mM stock solution. Aliquots of the stock solution were diluted with the DMEM medium described above and added to appropriate wells. Serial dilutions were made to give a range of test concentrations. Control wells to which test compound was not added were included on each plate. The plates were incubated overnight at 37°C in a humidified (7.5% CO_2 : 95% air) incubator.

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 denaturating solution (FixDenat solution, Boehringer Mannheim Catalogue No. 647 229; 50µl) was added to each well and the plates were placed on 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 plates were placed on a plate shaker at ambient temperature for 90 minutes. The wells were washed with PBS (x5) to ensure removal of non-bound antibody conjugate. The plates were blotted dry and tetramethylbenzidine substrate solution (Boehringer Mannheim Catalogue No. 647 229; 100µl) was added to each well. The plates were gently agitated on a plate shaker while the colour developed during a 10 to 20 minute period. The absorbance of the wells was measured at 690nm. The extent of inhibition of cellular proliferation at a range of concentrations of each test compound was determined and an anti-proliferative IC_{50} value was 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 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.

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 compounds were diluted from a 10mM stock solution in DMSO using RPMI medium as described above. Aliquots (10µl) of the diluted test compounds were transferred to the wells, again taking care not to disturb the microdroplets. The plates were incubated at 37°C in a humidified (7.5% CO_2 : 95% air) incubator for about 48 hours.

Migration was assessed visually and the distance of migration was measured back to the edge of the agar droplet. A migratory inhibitory IC_{50} 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 about 5 x 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.

(e) hERG-encoded Potassium Channel Assay

This assay determines the ability of a test compound to inhibit the tail current flowing through the hERG-encoded potassium channel.

Human embryonic kidney (HEK) cells expressing the hERG-encoded channel were grown in Eagle's Minimum Essential Medium (EMEM; Sigma-Aldrich catalogue number M2279), supplemented with 10% Foetal Calf Serum (Labtech International; product number 4-101-500), 10% M1 serum-free supplement (Egg Technologies; product number 70916) and 0.4 mg/ml Geneticin G418 (Sigma-Aldrich; catalogue number G7034). One or two days before each experiment, the cells were detached from the tissue culture flasks with Accutase (TCS Biologicals) using standard tissue culture methods. They were then put onto glass coverslips resting in wells of a 12 well plate and covered with 2 ml of the growing media.

For each cell recorded, a glass coverslip containing the cells was placed at the bottom of a Perspex chamber containing bath solution (see below) at ambient temperature (~20°C). This chamber was fixed to the stage of an inverted, phase-contrast microscope. Immediately after placing the coverslip in the chamber, bath solution was perfused into the chamber from a gravity-fed reservoir for 2 minutes at a rate of ~ 2 ml/minute. After this time, perfusion was stopped.

A patch pipette made from borosilicate glass tubing (GC120F, Harvard Apparatus) using a P-97 micropipette puller (Sutter Instrument Co.) was filled with pipette solution (see hereinafter). The pipette was connected to the headstage of the patch clamp amplifier

(Axopatch 200B, Axon Instruments) via a silver/silver chloride wire. The headstage ground was connected to the earth electrode. This consisted of a silver/silver chloride wire embedded in 3% agar made up with 0.85% sodium chloride.

The cell was recorded in the whole cell configuration of the patch clamp technique. Following "break-in", which was done at a holding potential of –80mV (set by the amplifier), and appropriate adjustment of series resistance and capacitance controls, electrophysiology software (*Clampex*, Axon Instruments) was used to set a holding potential (-80mV) and to deliver a voltage protocol. This protocol was applied every 15 seconds and consisted of a 1 s step to +40mV followed by a 1 s step to –50mV. The current response to each imposed voltage protocol was low pass filtered by the amplifier at 1kHz. The filtered signal was then acquired, on line, by digitising this analogue signal from the amplifier with an analogue to digital converter. The digitised signal was then captured on a computer running *Clampex* software (Axon Instruments). During the holding potential and the step to + 40mV the current was sampled at 1kHz. The sampling rate was then set to 5kHz for the remainder of the voltage protocol.

The compositions, pH and osmolarity of the bath and pipette solution are tabulated below.

Salt	Pipette (mM)	Bath (mM)
NaCl	-	137
KCl	130	4
$MgCl_2$	1	1
$CaCl_2$	-	1.8
HEPES	10	10
glucose	-	10
Na_2ATP	5	-
EGTA	5	-

Parameter	Pipette	Bath
pH	7.18 – 7.22	7.40
pH adjustment with	1M KOH	1M NaOH
Osmolarity (mOsm)	275-285	285-295

The amplitude of the hERG-encoded potassium channel tail current following the step from +40mV to –50mV was recorded on-line by *Clampex* software (Axon Instruments).

Following stabilisation of the tail current amplitude, bath solution containing the vehicle for the test substance was applied to the cell. Providing the vehicle application had no significant effect on tail current amplitude, a cumulative concentration effect curve to the compound was then constructed.

The effect of each concentration of test compound was quantified by expressing the tail current amplitude in the presence of a given concentration of test compound as a percentage of that in the presence of vehicle. Test compound potency (IC_{50}) was determined by fitting the percentage inhibition values making up the concentration-effect to a four parameter Hill equation using a standard data-fitting package. If the level of inhibition seen at the highest test concentration did not exceed 50%, no potency value was produced and a percentage inhibition value at that concentration was quoted.

Cytochrome P450 isoenzyme assays may be conducted by conventional means.

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

Test (a):- IC_{50} in the range, for example, 0.001 - 10 μM;

Test (b):- IC_{50} in the range, for example, 0.01 - 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, many of the particular compounds of the Formula I provided hereinafter as Examples possess activity at the following concentrations or doses in one or more of the above tests (a), (b), (c) and (d):-

Test (a):- IC_{50} in the range, for example, 0.001 - 0.1 μM;

Test (b):- IC_{50} in the range, for example, 0 01 - 1 μM;

Test (c):- activity in the range, for example, 0.1-1 μM;

Test (d):- activity in the range, for example, 1-200 mg/kg/day.

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 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.

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).

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

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 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 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.

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 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 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 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. 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 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 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 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 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.

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.

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 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 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 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 :-

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

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [Herceptin™] and the anti-erbB1 antibody cetuximab [C225]), farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for

example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function and angiostatin);

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

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

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

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

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 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

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 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 phase silica, for example on a Dynamax C-18 60Å 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 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 following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad;

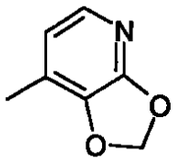
(vi) intermediates were not generally fully characterised and purity was assessed by thin layer chromatographic, HPLC, infra-red (IR) and/or NMR analysis;

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

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;

(xi) when describing the substituent on the amino group at the 4-position of the quinazoline ring in the Examples which follow, the following chemical nomenclature has been used '2,3-methylenedioxypyrid-4-yl' whereas, in the description and claims portions of the patent specification, that group is often described as a '2,3-methylenedioxypyridin-4-yl group'; for the avoidance of any doubt, it is to be understood that each of these terms relates to a group of formula



(x) the following abbreviations have been used:-

DMF	N,N-dimethylformamide
DMSO	dimethylsulphoxide
THF	tetrahydrofuran
DMA	N,N-dimethylacetamide

Example 1

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(3-chloropropoxy)-6-methoxyquinazoline

Sodium hexamethyldisilazane (1M solution in THF; 0.734 ml) was added to a solution of 4-amino-5-chloro-2,3-methylenedioxypyridine (0.12 g) in DMF (4 ml) that had been cooled to 0°C and the mixture was stirred for 15 minutes. A portion (0.1 g) of 4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline was added and the resultant mixture was stirred and allowed to warm to ambient temperature. The mixture was stirred at ambient temperature for 16 hours. The reaction mixture was evaporated and the residue was partitioned between methylene chloride and a saturated aqueous ammonium chloride solution. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent followed by increasingly polar mixtures of methylene chloride and acetonitrile. There was thus obtained the title compound as a white foam (0.11 g); NMR Spectrum: (DMSOd_6 and CD_3CO_2D) 2.3 (m, 2H), 3.8 (m, 2H), 4.05 (s, 3H), 4.4 (t, 2H), 6.3 (s, 2H), 7.4 (s, 1H), 7.9 (s, 1H), 8.15 (s, 1H), 8.95 (s, 1H); Mass Spectrum: $M+H^+$ 423 and 425.

The 4-amino-5-chloro-2,3-methylenedioxypyridine used as a starting material was prepared as follows :-

Bromochloromethane (20 ml) was added to a mixture 5-chloro-2,3-dihydroxypyridine (30 g), caesium carbonate (100 g) and DMF (300 ml) and the mixture was stirred and heated to 90°C for 3.5 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was purified by column chromatography on silica using methylene chloride as eluent. There was thus obtained 5-chloro-2,3-methylenedioxypyridine as a white solid (4.7 g); NMR Spectrum: (DMSOd_6) 6.25 (s, 2H), 7.5 (s, 1H), 7.65 (s, 1H).

A mixture of diisopropylamine (8.2 ml) and THF (100 ml) was cooled to -70°C and n-butyllithium (2.5 M in hexane, 24 ml) was added dropwise. The mixture was stirred at -70°C for a further 20 minutes. A solution of 5-chloro-2,3-methylenedioxypyridine (4.2 g) in THF (40 ml) was added over 10 minutes and the reaction mixture was stirred at -70°C for 1 hour. Dry carbon dioxide gas was bubbled into the reaction mixture for 30 minutes. The resultant reaction mixture was allowed to warm to ambient temperature. Water (20 ml) was added and the organic solvent was evaporated. The residue was acidified to pH2 by the

addition of 1N aqueous hydrochloric acid solution. The resultant solid was isolated and washed in turn with water and diethyl ether and dried under vacuum at 40°C. There was thus obtained 5-chloro-2,3-methylenedioxypyridine-4-carboxylic acid (3.6 g); ^{13}C NMR Spectrum: ($DMSOd_6$) 103, 120, 121, 138, 140, 158, 163.

A mixture of the material so obtained, diphenylphosphoryl azide (3.6 ml), anhydrous tert-butanol (13.5 ml), triethylamine (4.2 ml) and 1,4-dioxane (63 ml) was stirred and heated to 100°C for 3 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with water, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 9:1 mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained tert-butyl 5-chloro-2,3-methylenedioxypyrid-4-ylcarbamate (3.8 g); NMR Spectrum: ($DMSOd_6$) 1.45 (s, 9H), 6.2 (s, 2H), 7.7 (s, 1H), 9.2 (s, 1H).

The material so obtained was dissolved in methylene chloride (35 ml) and the solution was cooled to 0°C. Trifluoroacetic acid (15 ml) was added and the mixture was stirred at 0°C for 3 hours. The mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The solvent was evaporated and the residue was diluted with ice water and neutralised to pH7 by the addition of 2N aqueous sodium hydroxide solution whilst keeping the mixture temperature at 0°C. The resultant mixture was extracted with methylene chloride and the extract dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and diethyl ether as eluent. There was thus obtained 4-amino-5-chloro-2,3-methylenedioxypyridine (2 g); NMR Spectrum: ($DMSOd_6$) 6.1 (s, 2H), 6.2 (s, 2H), 7.45 (s, 1H); ^{13}C NMR Spectrum: ($DMSOd_6$) 100, 112, 125, 136, 138, 157; Mass Spectrum: $M+H^+$ 173.

The 4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline used as a starting material was prepared as follows :-

Ammonium formate (45 g) was added portionwise over 1.25 hours to a stirred mixture of 7-benzyloxy-6-methoxy-3,4-dihydroquinazolin-4-one (International Patent Application WO 02/16352, Example 1 thereof; 20 g), 10% palladium-on-carbon catalyst (3.3 g) and DMF (530 ml) and the reaction mixture was stirred for an additional 30 minutes. The catalyst was removed by filtration and the solvent was evaporated. There was thus obtained 7-hydroxy-6-methoxy-3,4-dihydroquinazolin-4-one (8.65 g); NMR Spectrum: ($DMSOd_6$) 3.9 (s, 3H), 7.0 (s, 1H), 7.45 (s, 1H), 7.9 (s, 1H).

A mixture of the material so obtained, acetic anhydride (63 ml) and pyridine (7.5 ml) was heated to 100°C for 4.5 hours. The resultant mixture was allowed to stand at ambient temperature for 16 hours. The mixture was poured into a stirred mixture (400 ml) of ice and water. The resultant precipitate was isolated and dried under vacuum. Analysis revealed that hydrolysis of the acetate group on the 4-position of the quinazoline was incomplete. The mixture was therefore further hydrolysed with water (150 ml) and pyridine (a few drops) at 90°C for 15 minutes. The resultant mixture was cooled to ambient temperature and the solid was collected by filtration, washed with water and dried under vacuum. There was thus obtained 7-acetoxy-6-methoxy-3,4-dihydroquinazolin-4-one (7.4 g); NMR Spectrum: ($DMSOd_6$) 2.3 (s, 3H), 3.9 (s, 3H), 7.45 (s, 1H), 7.65 (s, 1H), 8.05 (s, 1H).

A mixture of a portion (2 g) of the material so obtained, thionyl chloride (32 ml) and DMF (5 drops) was stirred and heated to reflux for 1.5 hours. The mixture was cooled to ambient temperature and the excess of thionyl chloride was evaporated. Toluene was added to the residue and evaporated. The resultant residue was diluted with methylene chloride (15 ml) and a 10:1 mixture (80 ml) of methanol and a saturated aqueous ammonium hydroxide solution was added. The resultant mixture was stirred and heated to 80°C for 10 minutes. The mixture was cooled to ambient temperature and evaporated. Water was added to the residue and the mixture was neutralised by the addition of dilute aqueous hydrochloric acid solution. The resultant precipitate was collected by filtration and dried under vacuum at 35°C for 16 hours. There was thus obtained 4-chloro-7-hydroxy-6-methoxyquinazoline (1.65 g); NMR Spectrum: ($DMSOd_6$) 4.0 (s, 3H), 7.25 (s, 1H), 7.4 (s, 1H), 8.8 (s, 1H).

Di-tert-butyl azodicarboxylate (2.3 g) was added portionwise over a few minutes to a stirred mixture of 4-chloro-7-hydroxy-6-methoxyquinazoline (1.65 g), 3-chloropropanol (0.7 ml), triphenylphosphine (2.6 g) and methylene chloride (100 ml) and the reaction mixture was stirred at ambient temperature for 2 hours. The mixture was concentrated to a volume of about 30 ml by evaporation and the residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p 40-60°C) and ethyl acetate as eluent. There was thus obtained 4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline as a white solid (2 g); NMR Spectrum: ($DMSOd_6$) 2.3 (m, 2H), 3.8 (m, 2H), 4.05 (s, 3H), 4.4 (m, 2H), 7.45 (s, 1H), 7.55 (s, 1H), 8.9 (s, 1H).

Example 2

7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxyquinazoline

Using an analogous procedure to that described in Example 1, 4-chloro-7-(2-chloroethoxy)-6-methoxyquinazoline was reacted with 4-amino-5-chloro-2,3-methylenedioxypyridine to give the title compound in 92% yield; NMR Spectrum: (DMSOd_6 and CD_3CO_2D) 4.05 (s, 3H), 4.1 (t, 2H), 4.55 (t, 2H), 6.3 (s, 2H), 7.4 (s, 1H), 7.9 (s, 1H), 8.15 (s, 1H), 8.95 (s, 1H); Mass Spectrum: $M+H^+$ 409 and 411.

The 4-chloro-7-(2-chloroethoxy)-6-methoxyquinazoline used as a starting material was prepared as follows :-

1,2-Dichloroethane (400 ml) was added to a stirred mixture of 7-hydroxy-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (International Patent Application WO 02/16352, Example 2, Note [4] thereof; 85 g), potassium carbonate (77 g) and DMF (400 ml) and the reaction mixture was heated to 70°C for 16 hours. The reaction mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the solid so obtained was washed with water and dried over phosphorus pentoxide at 50°C. The material so obtained was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. There was thus obtained 7-(2-chloroethoxy)-6-methoxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one as a white solid (65.6 g); NMR Spectrum: ($CDCl_3$) 1.2 (s, 9H), 3.9 (t, 2H), 4.0 (s, 3H), 4.4 (t, 2H), 5.95 (s, 2H), 7.1 (s, 1H), 7.7 (s, 1H), 8.2 (s, 1H); Mass Spectrum: $M+H^+$ 369 and 371.

A mixture of the material so obtained and a saturated solution of ammonia gas in methanol (1.6 L) was stirred at ambient temperature for 2 days. The solvent was concentrated by evaporation to about one-fourth of the original volume and the precipitate was collected by filtration and washed with diethyl ether There was thus obtained 7-(2-chloroethoxy)-6-methoxy-3,4-dihydroquinazolin-4-one as a white solid (44 g); NMR Spectrum: (DMSOd_6) 3.9 (s, 3H), 4.05 (t, 2H), 4.4 (t, 2H), 7.15 (s, 1H), 7.45 (s, 1H), 8.0 (s, 1H); Mass Spectrum: $M+H^+$ 255 and 257.

A mixture of a portion (5 g) of the material so obtained, thionyl chloride (28 ml) and DMF (0.7 ml) was stirred and heated to 80°C for 1.5 hours. The excess of thionyl chloride was evaporated and toluene was added and evaporated. The residual solid was suspended in a mixture of ice and water and basified to pH7.5 by the addition of 2N aqueous sodium hydroxide solution followed by a saturated aqueous sodium bicarbonate solution. The

resultant solid was collected by filtration, washed with water and diethyl ether and dried over over phosphorus pentoxide under vacuum. The material so obtained was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and acetonitrile as eluent. There was thus obtained 4-chloro-7-(2-chloroethoxy)-6-methoxyquinazoline (3.06 g); NMR Spectrum: ($CDCl_3$) 3.95 (t, 2H), 4.1 (s, 3H), 4.5 (t, 2H), 7.35 (s, 1H), 7.45 (s, 1H), 8.9 (s, 1H); Mass Spectrum: $M+H^+$ 273 and 275.

Example 3

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxy-7-[3-(4-prop-2-ynylpiperazin-1-yl)propoxy]quinazoline

A mixture of 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(3-chloropropoxy)-6-methoxyquinazoline (0.08 g), 1-prop-2-ynylpiperazine (0.047 g), potassium iodide (0.01 g) and DMA (2 ml) was stirred and heated to 80°C for 3.5 hours. The solvent was evaporated and the residue was partitioned between methylene chloride and a saturated aqueous ammonium chloride solution. The organic phase was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 19:1 mixture of methylene chloride and methanol and then a 9:1 mixture of methylene chloride and a saturated methanolic ammonia solution as eluent. The resulting gum was triturated under diethyl ether. There was thus obtained the title compound as a solid (0.066 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.3 (m, 2H), 3.2-3.6 (br m, 10H), 3.75 (s, 1H), 3.95 (br s, 2H), 4.0 (s, 3H), 4.35 (m, 2H), 6 3 (s, 2H), 7.4 (s, 1H), 7.9 (s, 1H), 8.15 (s, 1H), 8.95 (s, 1H); Mass Spectrum: $M+H^+$ 511 and 513.

The 1-prop-2-ynylpiperazine used as a starting material was prepared as follows :-

Propargyl bromide (80% solution in toluene; 40 ml) was added dropwise during 10 minutes to a stirred mixture of 1-tert-butoxycarbonylpiperazine (50 g), potassium carbonate (74.2 g) and acetonitrile (2 L) that had been cooled to 0°C. The mixture was stirred for 1.5 hours and allowed to warm to ambient temperature. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. There was thus obtained tert-butyl 4-prop-2-ynylpiperazine-1-carboxylate as an oil (45.5 g); NMR Spectrum: ($CDCl_3$) 1.4 (s, 9H), 2.2 (s, 1H), 2.45 (m, 4H), 3.3 (s, 2H), 3.45 (m, 4H).

A solution of the material so obtained in methylene chloride (100 ml) was added slowly to a solution of hydrogen chloride gas in 1,4-dioxane (4M, 450 ml). The reaction was

slightly exothermic and a precipitate formed as carbon dioxide gas was evolved. The mixture was stirred at ambient temperature for 1 hour. The resultant mixture was evaporated and the residue was suspended in methylene chloride. A solution of ammonia gas in methanol (7M, 110 ml) was added and the mixture was stirred at ambient temperature for 15 minutes. The mixture was filtered and the filtrate was evaporated. An oil was obtained which crystallised on standing. There was thus obtained 1-prop-2-ynylpiperazine (23 g); NMR Spectrum: ($CDCl_3$) 2.2 (s, 1H), 2.5 (br s, 4H), 2.85 (m, 4H), 3.25 (s, 2H).

Example 4

7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline

Using an analogous procedure to that described in Example 1, 4-chloro-7-(2-chloroethoxy)-5-tetrahydropyran-4-yloxyquinazoline was reacted with 4-amino-5-chloro-2,3-methylenedioxypyridine to give the title compound in 37% yield; NMR Spectrum: ($CDCl_3$) 2.0 (m, 2H), 2.3 (m, 2H), 3.65 (m, 2H), 3.9 (m, 2H), 4.1 (m, 2H), 4.4 (m, 2H), 4.8 (m, 1H), 6.2 (s, 2H), 6.65 (s, 1H), 6.9 (s, 1H), 7.8 (s, 1H), 8.6 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 479 and 481.

The 4-chloro-7-(2-chloroethoxy)-5-tetrahydropyran-4-yloxyquinazoline used as a starting material was prepared as follows :-

Di-tert-butyl azodicarboxylate (0.338 g) was added to a stirred mixture of 4-chloro-7-hydroxy-5-tetrahydropyran-4-yloxyquinazoline (International Patent Application WO 01/94341, Example 15, Note [10] thereof; 0.25 g), 2-chloroethanol (0.073 ml), triphenylphosphine (0.385 g) and methylene chloride (15 ml) and the reaction mixture was stirred at ambient temperature for 1 hour. The mixture was concentrated to a volume of about 5 ml by evaporation and the residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p 40-60°C) and ethyl acetate as eluent. There was thus obtained 4-chloro-7-(2-chloroethoxy)-5-tetrahydropyran-4-yloxyquinazoline as a solid (0.17 g); NMR Spectrum: ($CDCl_3$) 2.0 (m, 2H), 2.15 (m, 2H), 3.7 (m, 2H), 3.95 (t, 2H), 4.1 (m, 2H), 4.4 (t, 2H), 4.8 (m, 1H), 6.7 (s, 1H), 6.95 (s, 1H), 8.85 (s, 1H).

Example 5

7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline

Using an analogous procedure to that described in Example 1, 4-chloro-7-(2-chloroethoxy)-5-isopropoxyquinazoline was reacted with 4-amino-5-chloro-2,3-methylenedioxypyridine to give the title compound in 86% yield; NMR Spectrum: ($CDCl_3$) 1.55 (d, 6H), 3.9 (t, 2H), 4.4 (t, 2H), 4.9 (m, 1H), 6.2 (s, 2H), 6.6 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.65 (s, 1H); Mass Spectrum: $M+H^+$ 437 and 439.

The 4-chloro-7-(2-chloroethoxy)-5-isopropoxyquinazoline used as a starting material was prepared as follows :-

Di-tert-butyl azodicarboxylate (28.9 g) was added to a stirred mixture of 7-benzyloxy-5-hydroxy-3-pivaloyloxymethyl-3,4-dihydroquinazolin-4-one (International Patent Application WO 01/94341, Example 15, Note [8] thereof; 30 g), isopropanol (7.3 ml), triphenylphosphine (32.95 g) and methylene chloride (350 ml) that had been cooled to 0°C. The reaction mixture was allowed to warm to ambient temperature and was stirred for 1.5 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained 7-benzyloxy-5-isopropoxy-3,4-dihydroquinazolin-4-one as a solid (23.8 g); NMR Spectrum: ($DMSOd_6$) 7.89 (s, 1H), 7.5-7.3 (m, 5H), 6.75 (s, 1H), 6.62 (s, 1H), 5.24 (s, 2H), 4.65 (m, 1H), 1.29 (d, 6H).

Ammonium formate (48.4 g) was added to a stirred mixture of 7-benzyloxy-5-isopropoxy-3,4-dihydroquinazolin-4-one (23.8 g), 10% palladium-on-carbon catalyst (2.8 g) and DMF (300 ml) and the resultant mixture was stirred at ambient temperature for 2 hours. The mixture was filtered and the filtrate was evaporated. The material so obtained was triturated under water, the pH of which was adjusted to pH7. The solid so obtained was collected by filtration, washed with water and with diethyl ether and dried over phosphorus pentoxide under vacuum. There was thus obtained 7-hydroxy-5-isopropoxy-3,4-dihydroquinazolin-4-one as a white solid (15.9 g); NMR Spectrum: ($DMSOd_6$) 1.3 (d, 6H), 4.57 (m, 1H), 6.42 (s, 1H), 6.5 (s, 1H), 7.8 (s, 1H).

A mixture of the material so obtained, acetic anhydride (34 ml) and pyridine (0.62 ml) was heated to 70°C for 30 minutes. The reaction mixture was cooled to ambient temperature and the excess of acetic anhydride was evaporated. The white solid so obtained was added to hot water (80°C, 250 ml) and the mixture was stirred vigorously

and heated to 80°C for 20 minutes. The mixture was cooled to ambient temperature and the solid was isolated and dried over phosphorus pentoxide. There was thus obtained 7-acetoxy-5-isopropoxy-3,4-dihydroquinazolin-4-one (17.86 g); NMR Spectrum: ($DMSOd_6$) 7.97 (s, 1H), 6.91 (s, 1H), 6.85 (s, 1H), 4.65 (m, 1H), 2.32 (s, 3H), 1.33 (d, 6H).

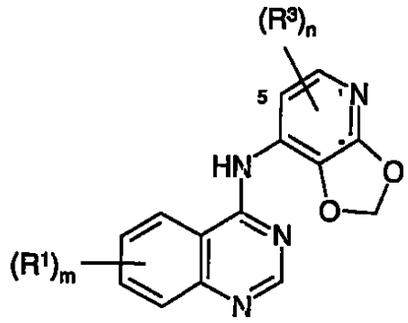
A mixture of a portion (5.4 g) of the material so obtained, triphenylphosphine (10.8 g), carbon tetrachloride (12 ml) and 1,2-dichloroethane (50 ml) was stirred and heated to 70°C for 2 hours. The mixture was cooled to ambient temperature and the solvent was evaporated. The residue was dissolved in a 0.5M solution of ammonia gas in 1,4-dioxane (250 ml) and the mixture was heated to 70°C for 10 minutes. The solvent was evaporated and the residue was cooled in an ice-water bath. Methylene chloride and water were added and the aqueous layer was brought to pH7 by the addition of dilute aqueous hydrochloric acid. The mixture was filtered. The organic phase was dried over magnesium sulphate and evaporated to give 4-chloro-7-hydroxy-5-isopropoxyquinazoline as a foam which was used without further purification

Di-tert-butyl azodicarboxylate (7.9 g) was added to a stirred mixture of the 4-chloro-7-hydroxy-5-isopropoxyquinazoline so obtained, 2-chloroethanol (1.5 ml), triphenylphosphine (8 g) and methylene chloride (200 ml) and the reaction mixture was stirred at ambient temperature for 4 hours. The mixture was concentrated by evaporation and the residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p 40-60°C) and ethyl acetate as eluent. There was thus obtained 4-chloro-7-(2-chloroethoxy)-5-isopropoxyquinazoline (2.5 g); NMR Spectrum: ($CDCl_3$) 1.45 (d, 6H), 3.9 (t, 2H), 4.4 (t, 2H), 4.75 (m, 1H), 6.65 (s, 1H), 6.9 (s, 1H), 8.8 (s, 1H).

Example 6

Using an analogous procedure to that described in Example 3, the appropriate 7-haloalkoxyquinazoline was reacted with the appropriate heterocyclic compound to give the compounds described in Table I. Unless otherwise stated, each compound described in Table I was obtained as a free base.

Table I



Compound No. & Note	$(R^1)_m$	$(R^3)_n$
[1]	6-methoxy-7-[3-(4-isobutyrylpiperazin-1-yl)propoxy]	5-chloro
[2]	6-methoxy-7-{3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy}	5-chloro
[3]	6-methoxy-7-[2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]	5-chloro
[4]	5-tetrahydropyran-4-yloxy-7-[2-(4-acetylpiperazin-1-yl)ethoxy]	5-chloro
[5]	5-tetrahydropyran-4-yloxy-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy}	5-chloro
[6]	5-isopropoxy-7-[2-(4-acetylpiperazin-1-yl)ethoxy]	5-chloro
[7]	5-isopropoxy-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy}	5-chloro
[8]	6-(2-morpholinoethoxy)-7-methoxy	5-chloro
[9]	6-[2-(4-methylpiperazin-1-yl)ethoxy]-7-methoxy	5-chloro
[10]	6-(2-pyrrolidin-1-ylethoxy)-7-methoxy	5-chloro
[11]	6-[2-(4-acetylpiperazin-1-yl)ethoxy]-7-methoxy	5-chloro
[12]	6-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy}-7-methoxy	5-chloro
[13]	6-(3-pyrrolidin-1-ylpropoxy)-7-methoxy	5-chloro
[14]	6-(3-morpholinopropoxy)-7-methoxy	5-chloro
[15]	6-[3-(4-acetylpiperazin-1-yl)propoxy]-7-methoxy	5-chloro
[16]	6-[3-(4-methylpiperazin-1-yl)propoxy]-7-methoxy	5-chloro

[17]	6-{3-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]propoxy}-7-methoxy	5-chloro
[18]	5-tetrahydropyran-4-yloxy-7-[2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]	5-chloro
[19]	5-tetrahydropyran-4-yloxy-7-(2-morpholinoethoxy)	5-chloro
[20]	5-tetrahydropyran-4-yloxy-7-(3-morpholinopropoxy)	5-chloro
[21]	5-tetrahydropyran-4-yloxy-7-[3-(4-prop-2-ynylpiperazin-1-yl)propoxy]	5-chloro
[22]	5-isopropoxy-7-(2-piperazin-1-ylethoxy)	5-chloro
[23]	5-isopropoxy-7-{2-[4-(2-hydroxyethyl)piperazin-1-yl]ethoxy}	5-chloro
[24]	5-isopropoxy-7-(2-pyrrolidin-1-ylethoxy)	5-chloro
[25]	5-isopropoxy-7-(2-piperidinoethoxy)	5-chloro
[26]	5-isopropoxy-7-(2-morpholinoethoxy)	5-chloro
[27]	5-isopropoxy-7-[2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]	5-chloro
[28]	5-isopropoxy-6-{2-[(3RS,4SR)-3,4-dimethoxypyrrolidin-1-yl]ethoxy}	5-chloro
[29]	6-{2-[(3RS,4SR)-3,4-ethylidenedioxypyrrolidin-1-yl]ethoxy}-5-isopropoxy	5-chloro
[30]	5-isopropoxy-7-[2-(4-methylpiperazin-1-yl)ethoxy]	5-chloro
[31]	5-isopropoxy-7-(3-morpholinopropoxy)	5-chloro
[32]	7-(3-morpholinopropoxy)	5-chloro
[33]	7-[3-(4-acetylpiperazin-1-yl)propoxy]	5-chloro
[34]	6-methoxy-7-[2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]	hydrogen
[35]	6-methoxy-7-[3-(4-prop-2-ynylpiperazin-1-yl)propoxy]	hydrogen

Notes

[1] The reactants were 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(3-chloropropoxy)-6-methoxyquinazoline and 1-isobutyrylpiperazine. The reaction mixture was heated to 120°C for 3 hours. The reaction product was purified by column chromatography on a C18 reversed phase silica column (Waters Symmetry column, 5 microns silica, 19 mm diameter, 100 mm length) using a decreasingly polar mixture of

water and acetonitrile (containing 1% acetic acid) as eluent. The material so obtained was dissolved in methylene chloride and an ion exchange resin (diethylaminopolystyrene resin, 4 equivalents) was added and the mixture was stirred for 30 minutes. The mixture was filtered and the filtrate was evaporated. The resultant residue was triturated under pentane to give the required product in 51% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.1 (d, 6H), 2.1 (m, 2H), 2.45 (m, 4H), 2.55 (m, 2H), 2.75 (m, 1H), 3.5 (m, 2H), 3.6 (m, 2H), 4.0 (s, 3H), 4.25 (t, 2H), 6.1 (s, 2H), 7.1 (br s, 1H), 7.3 (s, 1H), 7.75 (s, 1H), 8.7 (br s, 1H); Mass Spectrum. $M+H^+$ 543 and 545.

The 1-isobutyrylpiperazine used as a starting material was prepared as follows :-

Isobutyryl chloride (3.25 ml) was added dropwise to a stirred mixture of 1-benzylpiperazine (5 g), triethylamine (4.35 ml) and methylene chloride (75 ml) which was cooled to 0°C. The reaction mixture was allowed to warm to ambient temperature and stirred for 1 hour. The mixture was partitioned between methylene chloride and water. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 3:2 mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained 1-benzyl-4-isobutyrylpiperazine (5.95 g) as an oil; NMR Spectrum: ($CDCl_3$) 1.1 (d, 6H), 2.45 (m, 4H), 2.8 (m, 1H), 3.5 (m, 4H), 3.65 (m, 2H), 7.3 (m, 5H); Mass Spectrum: $M+H^+$ 247.

A mixture of the material so obtained, cyclohexene (70 ml), palladium oxide-on-carbon catalyst (20%; 1.1 g) and ethanol (120 ml) was stirred and heated to 80°C for 3 hours. The catalyst was removed by filtration and the solvent was evaporated to give 1-isobutyrylpiperazine (3.7 g) as a solid; NMR Spectrum: ($CDCl_3$) 1.05 (d, 6H), 2.75 (m, 1H), 2.8 (m, 4H), 3.45 (m, 2H), 3.55 (m, 2H).

[2] The reactants were 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(3-chloropropoxy)-6-methoxyquinazoline and 1-(2,2,2-trifluoroethyl)piperazine. The reaction mixture was heated to 120°C for 3 hours. The reaction product was purified by column chromatography on a C18 reversed phase silica column (Waters Symmetry column, 5 microns silica, 19 mm diameter, 100 mm length) using a decreasingly polar mixture of water and acetonitrile (containing 1% acetic acid) as eluent. The material so obtained was dissolved in methylene chloride and an ion exchange resin (diethylaminopolystyrene resin, 4 equivalents) was added and the mixture was stirred for 30 minutes. The mixture was filtered and the filtrate was evaporated. The resultant residue was triturated under pentane to give the required product in 72% yield which gave the following characterising data; NMR

Spectrum: ($CDCl_3$) 2.1 (m, 2H), 2.5 (m, 6H), 2.7 (m, 4H), 2.95 (q, 2H), 4.05 (s, 3H), 4.25 (t, 2H), 6.1 (s, 2H), 7.1 (br s, 1H), 7.3 (s, 1H), 7.75 (s, 1H), 8.35 (br s, 1H); Mass Spectrum: $M+H^+$ 555 and 557; Elemental Analysis: Found C, 51.8; H, 5.0; N, 14.8; $C_{24}H_{26}ClF_3N_6O_4$ requires C, 51.9; H, 4.7; N, 15.1%.

The 1-(2,2,2-trifluoroethyl)piperazine used as a starting material was prepared as follows :-

2,2,2-Trifluoroethyl trifluoromethanesulphonate (8.2 g) was added to a stirred mixture of 1-tert-butoxycarbonylpiperazine (6 g), potassium carbonate (5.77 g) and acetonitrile (30 ml) and the resultant mixture was stirred at ambient temperature for 16 hours. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p 40-60°C) and ethyl acetate as eluent. There was thus obtained tert-butyl 4-(2,2,2-trifluoroethylpiperazine-1-carboxylate as a solid (8.1 g); NMR Spectrum: ($CDCl_3$) 1.45 (s, 9H), 2.6 (m, 4H), 2.95 (q, 2H), 3.4 (m, 4H).

Hydrogen chloride gas was bubbled through a solution of tert-butyl 4-(2,2,2-trifluoroethylpiperazine-1-carboxylate (8 g) in ethyl acetate (50 ml) during 1.5 hours. A precipitate formed as carbon dioxide gas was evolved. The precipitate was collected by filtration, washed with ethyl acetate and dried under vacuum. There was thus obtained 1-(2,2,2-trifluoroethyl)piperazine hydrochloride (7 g); NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2 85 (m, 4H), 3.1 (m, 4H), 3.35 (q, 2H).

The material so obtained was suspended in methylene chloride and a saturated methanolic ammonia solution (20 ml) was added. The resultant mixture was stirred at ambient temperature for 20 minutes. The mixture was filtered and the filtrate was evaporated at ambient temperature under vacuum. There was thus obtained 1-(2,2,2-trifluoroethyl)piperazine which was used without any additional purification.

[3] The reactants were 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxyquinazoline and 1-prop-2-ynylpiperazine. The required product was obtained in 52% yield and gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 3.3 (br s, 4H), 3.6 (br s, 4H), 3.75 (br s, 3H), 3.95 (s, 2H), 4.05 (s, 3H), 4.65 (t, 2H), 6.3 (s, 2H), 7.5 (s, 1H), 7.9 (s, 1H), 8.2 (s, 1H), 9.0 (s, 1H); Mass Spectrum: $M+H^+$ 497 and 499; Elemental Analysis: Found C, 56 3; H, 5.4; N, 16.2; $C_{24}H_{25}ClN_6O_4$ $0.7H_2O$ requires C, 56.6; H, 5.2; N, 16.5%.

[4] The reactants were 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline and 1-acetylpiperazine. The reaction mixture was heated to 80°C for 3 hours and then to 110°C for 5 hours. The reaction product was purified by column chromatography on a C18 reversed phase silica column (Waters Symmetry column, 5 microns silica, 19 mm diameter, 100 mm length) using a decreasingly polar mixture of water and acetonitrile (containing 1% acetic acid) as eluent. The organic solvents were evaporated and the pH of the aqueous phase was adjusted to 7.5. The solution was extracted with methylene chloride and the organic phase was dried over magnesium sulphate and evaporated. The resultant residue was triturated under diethyl ether to give the required product in 45% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.0 (m, 2H), 2.1 (s, 3H), 2.3 (m, 2H), 2.6 (m, 4H), 2.95 (m, 2H), 3.55 (m, 2H), 3.65 (m, 4H), 4.1 (m, 2H), 4.3 (m, 2H), 4.8 (m, 1H), 6.2 (s, 2H), 6 6 (s, 1H), 6.9 (s, 1H), 7.8 (s, 1H), 8.65 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 571 and 573; Elemental Analysis: Found C, 55.3; H, 5.4; N, 13.9; $C_{27}H_{31}ClN_6O_6 \cdot 1H_2O$ requires C, 55.1; H, 5.7; N, 14.3.

[5] The reactants were 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline and (3RS,4SR)-3,4-methylenedioxypyrrolidine. The reaction mixture was heated to 80°C for 3 hours and then to 110°C for 5 hours. The reaction product was purified by column chromatography on a C18 reversed phase silica column (Waters Symmetry column, 5 microns silica, 19 mm diameter, 100 mm length) using a decreasingly polar mixture of water and acetonitrile (containing 1% acetic acid) as eluent. The organic solvents were evaporated and the pH of the aqueous phase was adjusted to 7.5. The solution was extracted with methylene chloride and the organic phase was dried over magnesium sulphate and evaporated. The resultant residue was triturated under diethyl ether to give the required product in 69% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.0 (m, 2H), 2.3 (m, 2H), 2.4 (m, 2H), 2.3 (t, 2H), 3.3 (d, 2H), 3.55 (m, 2H), 4.1 (m, 2H), 4.3 (t, 2H), 4.65 (m, 2H), 4.8 (m, 1H), 4.9 (s, 1H), 5.2 (s, 1H), 6.2 (s, 2H), 6.6 (s, 1H), 6.9 (s, 1H), 7.8 (s, 1H), 8.65 (s, 1H), 9.5 (s, 1H); Mass Spectrum: $M+H^+$ 558 and 560; Elemental Analysis: Found C, 56.5; H, 5.3; N, 12.5; $C_{26}H_{28}ClN_5O_7$ $0.2Et_2O$ requires C, 56.2; H, 5.3; N, 12.2%.

The (3RS,4SR)-3,4-methylenedioxypyrrolidine used as a starting material was prepared as follows :-

A solution of di-tert-butyl dicarbonate (Boc_2O, 78.95 g) in ethyl acetate (125 ml) was added dropwise to a stirred mixture of 3-pyrroline (25 g; 65% pure containing

pyrrolidine) and ethyl acetate (125 ml) which had been cooled to 0°C. The reaction temperature was maintained at 5-10°C during the addition. The resultant reaction mixture was allowed to warm to ambient temperature overnight. The reaction mixture was washed successively with water, 0.1N aqueous hydrochloric acid solution, water, a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated. There was thus obtained, as a colorless oil (62 g), a 2:1 mixture of tert-butyl 3-pyrroline-1-carboxylate, NMR: ($CDCl_3$) 1.45 (s, 9H), 4.1 (d, 4H), 6.75 (m, 2H), and tert-butyl pyrrolidine-1-carboxylate, NMR: ($CDCl_3$) 1.5 (s, 9H), 1.8 (br s, 4H), 3.3 (br s, 4H).

A solution of the mixture of materials so obtained in acetone (500 ml) was added dropwise to a mixture of N-methylmorpholine-N-oxide (28.45 g), osmium tetroxide (1 g) and water (500 ml) whilst keeping the reaction temperature below 25°C. The reaction mixture was then stirred at ambient temperature for 5 hours. The solvent was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent and by further column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol. There was thus obtained tert-butyl (3RS,4SR)-3,4-dihydroxypyrrolidine-1-carboxylate as an oil (34.6 g); NMR Spectrum: ($CDCl_3$) 1.45 (s, 9H), 2.65 (m, 2H), 3.35 (m, 2H), 3.6 (m, 2H), 4.25 (m, 2H).

A solution of tert-butyl (3RS,4SR)-3,4-dihydroxypyrrolidine-1-carboxylate (34.6 g) in DMF (400 ml) was cooled to 0-5°C and sodium hydride (60% dispersion in mineral oil, 0.375 mol) was added portionwise. The reaction mixture was stirred at 5°C for 1 hour. Dibromomethane (15.6 ml) was added and the reaction mixture was stirred at 5°C for 30 minutes. The reaction mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The DMF was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained tert-butyl (3RS,4SR)-3,4-methylenedioxypyrrolidine-1-carboxylate as a colourless oil (19.77 g);NMR Spectrum: ($CDCl_3$) 1.45 (s, 9H), 3.35 (m, 2H), 3.75 (br s, 2H), 4.65 (m, 2H), 4.9 (s, 1H), 5.1 (s, 1H).

A cooled 5M solution of hydrogen chloride in isopropanol (150 ml) was added to a solution of tert-butyl (3RS,4SR)-3,4-methylenedioxypyrrolidine-1-carboxylate (19 7 g) in methylene chloride (500 ml) that was cooled in an ice bath. The reaction mixture was allowed to warm to ambient temperature and was stirred for 4 hours. The solvent was evaporated and the residue was triturated under diethyl ether. The precipitate was collected by filtration, washed with diethyl ether and dried. There was thus obtained (3RS,4SR)-3,4-methylenedioxypyrrolidine hydrochloride as a beige solid (13.18 g); NMR Spectrum: ($DMSOd_6$) 3.15 (m, 2H), 3.35 (m, 2H), 4.65 (s, 1H), 4.8 (m, 2H), 5.1 (s, 1H).

The material so obtained was suspended in diethyl ether and a saturated methanolic ammonia solution was added The resultant mixture was stirred at ambient temperature for 10 minutes. The mixture was filtered and the solvent was evaporated at ambient temperature under vacuum. There was thus obtained (3RS,4SR)-3,4-methylenedioxypyrrolidine which was used without any additional purification.

[6] The reactants were 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline and 1-acetylpiperazine. The reaction mixture was heated to 85°C for 8 hours. The reaction product was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. The product was obtained in 89% yield and gave the following characterising data; m.p. 208-210°C; NMR Spectrum: ($CDCl_3$) 1.55 (d, 6H), 2.1 (s, 3H), 2.6 (m, 4H), 2.9 (t, 2H), 3.5 (t, 2H), 3.7 (t, 2H), 4.25 (t, 2H), 4.85 (m, 1H), 6.15 (s, 2H), 6.55 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Mass Spectrum: $M+H^+$ 529 and 531; Elemental Analysis: Found C, 57.0; H, 5.7; N, 15.7; $C_{25}H_{29}ClN_6O_5$ requires C, 56.8; H, 5.5; N, 15.9%.

[7] The reactants were 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline and (3RS,4SR)-3,4-methylenedioxypyrrolidine. The reaction mixture was heated to 95°C for 3 hours. The reaction product was purified by column chromatography on a C18 reversed phase silica column (Waters Symmetry column, 5 microns silica, 19 mm diameter, 100 mm length) using a decreasingly polar mixture of water and acetonitrile (containing 1% acetic acid) as eluent. The organic solvents were evaporated and the pH of the aqueous phase was adjusted to 7. The solution was extracted with methylene chloride and the organic phase was dried over magnesium sulphate and evaporated. The resultant residue was triturated under diethyl ether to give the required product in 64% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.55 (d, 6H), 2.35 (m, 2H), 2.9 (t, 2H), 3.25 (d, 2H), 4.25 (t, 2H), 4.6 (m, 2H), 4 85 (m, 1H),

4.9 (s, 1H), 5.15 (s, 1H), 6.15 (s, 2H), 6.55 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Mass Spectrum: $M+H^+$ 516 and 518; Elemental Analysis: Found C, 54 7; H, 5.2; N, 13.2; $C_{24}H_{26}ClN_5O_6$ $0.5H_2O$ requires C, 54.9; H, 5.2; N, 13.3%.

[8] The reactants were 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-(2-chloroethoxy)-7-methoxyquinazoline (the preparation of which is described in Example 7 hereinafter) and morpholine. The reaction mixture was heated to 120°C for 16 hours. The required product was obtained in 69% yield and gave the following characterising data; NMR Spectrum: ($CDCl_3$ and CD_3CO_2D) 3.3 (m, 4H), 3.5 (t, 2H), 3.95 (m, 4H), 4.05 (s, 3H), 4.6 (t, 2H), 6.15 (s, 2H), 7.6 (s, 1H), 7.8 (s, 2H), 8.6 (s, 1H); Mass Spectrum: $M+H^+$ 460 and 462; Elemental Analysis: Found C, 53.45; H, 4.8; N, 14.5; $C_{21}H_{22}ClN_5O_5$ $0.55H_2O$ requires C, 53.7; H, 5.0; N, 14.9%.

[9] The reactants were 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-(2-chloroethoxy)-7-methoxyquinazoline and 1-methylpiperazine. The reaction mixture was heated to 120°C for 16 hours. The reaction product was purified by column chromatography on a Waters X-Terra silica column (C18 reversed-phase, 5 microns, 19 mm diameter, 100 mm length; Waters Inc., Milford, MA01757, USA) and eluted with decreasingly polar mixtures of an ammonium carbonate buffer (2 g/L in water) and acetonitrile. Appropriate fractions were collected, the organic solvent was evaporated and the resultant mixture was partitioned between ethyl acetate and a saturated aqueous sodium bicarbonate solution. The organic phase was dried over magnesium sulphate and evaporated. There was thus obtained the required product in 29% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$ and CD_3CO_2D) 2.7 (s, 3H), 3.25-3.35 (br m, 10H), 4.05 (s, 3H), 4.45 (t, 2H), 6.15 (s, 2H), 7.55 (s, 1H), 7.7 (s, 1H), 7.8 (s, 1H), 8.65 (s, 1H); Mass Spectrum: $M+H^+$ 473 and 475; Elemental Analysis: Found C, 54.9; H, 5.3; N, 17.1; $C_{22}H_{25}ClN_6O_4$ $0.4H_2O$ requires C, 55.0; H, 5.4; N, 17.5%.

[10] The reactants were 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-(2-chloroethoxy)-7-methoxyquinazoline and pyrrolidine. The reaction mixture was heated to 120°C for 16 hours. The required product was obtained in 41% yield and gave the following characterising data; NMR Spectrum: ($CDCl_3$ and CD_3CO_2D) 2.15 (m, 4H), 3.3-3.6 (br s, 4H), 3.7 (t, 2H), 4.05 (s, 3H), 4.65 (t, 2H), 6.15 (s, 2H), 7.65 (s, 1H), 7.8 (s, 1H), 7 9 (s, 1H), 8.65 (s, 1H); Mass Spectrum: $M+H^+$ 444 and 446, Elemental Analysis: Found C, 55.0; H, 5.0; N, 14.9; $C_{21}H_{22}ClN_5O_4$ $0.7H_2O$ requires C, 55.25; H, 5.2; N, 15.3%.

[11] The reactants were 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-(2-chloroethoxy)-7-methoxyquinazoline and 1-acetylpiperazine. The reaction mixture was heated to 120°C for 16 hours. The required product was obtained in 51% yield and gave the following characterising data; NMR Spectrum: ($CDCl_3$ and CD_3CO_2D) 2.15 (s, 3H), 3.1 (m, 2H), 3.2 (m, 2H), 3.4 (t, 2H), 3.75 (m, 2H), 3.85 (m, 2H), 4.0 (s, 3H), 4.55 (t, 2H), 6.15 (s, 2H), 7.6 (s, 1H), 7.7 (s, 1H), 7.8 (s, 1H), 8.6 (s, 1H); Mass Spectrum: $M+H^+$ 501 and 503.

[12] The reactants were 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-(2-chloroethoxy)-7-methoxyquinazoline and (3RS,4SR)-3,4-methylenedioxypyrrolidine. The reaction mixture was heated to 120°C for 16 hours. The required product was obtained in 73% yield and gave the following characterising data; NMR Spectrum: ($CDCl_3$ and CD_3CO_2D) 2.95 (m, 2H), 3.45 (t, 2H), 3.65 (d, 2H), 4.05 (s, 3H), 4.55 (t, 2H), 4.8 (m, 3H), 5.2 (s, 1H), 6.15 (s, 2H), 7.6 (s, 1H), 7.75 (s, 1H), 7.8 (s, 1H), 8.65 (s, 1H); Mass Spectrum: $M+H^+$ 488 and 490.

[13] The reactants were 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-(3-chloropropoxy)-7-methoxyquinazoline (the preparation of which is described in Example 8 hereinafter) and pyrrolidine. The reaction mixture was heated to 120°C for 16 hours. The required product was obtained in 50% yield and gave the following characterising data; NMR Spectrum: ($CDCl_3$ and CD_3CO_2D) 2.1 (m, 4H), 2.4 (m, 2H), 3.0-3.8 (br s, 4H), 3.4 (t, 2H), 4.05 (s, 3H), 4.35 (t, 3H), 6.1 (s, 2H), 7.6 (s, 1H), 7.75 (s, 1H), 7.8 (s, 1H), 8.65 (s, 1H); Mass Spectrum: $M+H^+$ 458 and 460; Elemental Analysis: Found C, 57.3; H, 5.4; N, 14.5; $C_{22}H_{24}ClN_5O_4$ $0.15H_2O$ requires C, 57.4; H, 5.3; N, 15.2%

[14] The reactants were 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-(3-chloropropoxy)-7-methoxyquinazoline and morpholine. The reaction mixture was heated to 120°C for 16 hours. The required product was obtained in 72% yield and gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.1 (m, 2H), 2.5 (m, 4H), 2.6 (t, 2H), 3.7 (m, 4H), 4.05 (s, 3H), 4.25 (t, 2H), 6.1 (s, 2H), 7.05 (s, 1H), 7.15 (s, 1H), 7.3 (s, 1H), 7.75 (s, 1H), 8.7 (s, 1H); Mass Spectrum: $M+H^+$ 474 and 476.

[15] The reactants were 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-(3-chloropropoxy)-7-methoxyquinazoline and 1-acetylpiperazine. The reaction mixture was heated to 120°C for 16 hours. The required product was obtained in 39% yield and gave the following characterising data; NMR Spectrum: ($CDCl_3$ and CD_3CO_2D) 2.15 (s, 3H), 2.35 (m, 2H), 3.15-3.3 (m, 6H), 3.8 (m, 2H), 3.9 (m, 2H), 4.0 (s, 3H), 4.3 (t, 2H), 6.15 (s, 2H), 7.6 (s, 1H), 7.65 (s, 1H), 7.8 (s, 1H), 8.65 (s, 1H); Mass Spectrum: $M+H^+$ 515 and 517.

[16] The reactants were 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-(3-chloropropoxy)-7-methoxyquinazoline and 1-acetylpiperazine. The reaction mixture was heated to 120°C for 16 hours. The required product was obtained in 27% yield and gave the following characterising data; NMR Spectrum: ($CDCl_3$ and CD_3CO_2D) 2.3 (m, 2H), 2.7 (s, 3H), 3.3 (t, 2H), 3.4 (m, 4H), 3.5 (m, 4H), 4.0 (s, 3H), 4.3 (t, 2H), 6.15 (s, 2H), 7.6 (s, 1H), 7.65 (s, 1H), 7.8 (s, 1H), 8.65 (s, 1H); Mass Spectrum: $M+H^+$ 487 and 489.

[17] The reactants were 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-(3-chloropropoxy)-7-methoxyquinazoline and (3RS,4SR)-3,4-methylenedioxypyrrolidine. The reaction mixture was heated to 95°C for 3 hours. The reaction product was purified by column chromatography on a C18 reversed phase silica column (Waters Symmetry column, 5 microns silica, 19 mm diameter, 100 mm length) using a decreasingly polar mixture of water and acetonitrile (containing 1% acetic acid) as eluent. The organic solvents were evaporated and the pH of the aqueous phase was adjusted to 7. The solution was extracted with methylene chloride and the organic phase was dried over magnesium sulphate and evaporated. The resultant residue was triturated under diethyl ether to give the required product in 57% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$ and CD_3CO_2D) 2.3 (m, 2H), 3.3 (m, 2H), 3.4 (t, 2H), 3.6 (d, 2H), 4.0 (s, 3H), 4.3 (t, 2H), 4.8 (m, 3H), 5.2 (s, 1H), 6.15 (s, 2H), 7.55 (s, 1H), 7.6 (s, 1H), 7.8 (s, 1H), 8.6 (s, 1H); Mass Spectrum: $M+H^+$ 502 and 504.

[18] The reactants were 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(2-chloroethoxy)-5-tetrahydropyran-4-yloxyquinazoline and 1-prop-2-ynylpiperazine. The reaction mixture was heated to 80°C for 3 hours and then to 110°C for 5 hours. The reaction product was purified by column chromatography on a Waters X-Terra silica column (C18 reversed-phase, 5 microns, 19 mm diameter, 100 mm length) and eluted with decreasingly polar mixtures of an ammonium carbonate buffer (2 g/L in water) and acetonitrile. Appropriate fractions were collected, the organic solvent was evaporated and the resultant mixture was partitioned between ethyl acetate and a saturated aqueous sodium bicarbonate solution. The organic phase was dried over magnesium sulphate and evaporated. There was thus obtained the required product in 54% yield which gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CD_3CO_2D) 1.85 (m, 2H), 2.15 (m, 2H), 2.5-3.0 (m, 10H), 3.15 (s, 1H), 3.3 (s, 2H), 3.55 (t, 2H), 3.9 (m, 2H), 4.3 (m, 2H), 5.05 (m, 1H), 6.2 (s, 2H), 6.9 (s, 2H), 7.8 (s, 1H), 8.5 (s, 1H); Mass Spectrum: $M+H^+$ 567 and 569; Elemental Analysis: Found C, 55.9; H, 5.6; N, 14.0; $C_{28}H_{31}ClN_6O_5$ $2H_2O$ requires C, 55.8; H, 5.85; N, 13.9%.

[19] Using the detailed conditions described in Note [18] immediately above, 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(2-chloroethoxy)-5-tetrahydropyran-4-yloxyquinazoline was reacted with morpholine to give the required product in 48% yield which gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CD_3CO_2D) 1.8 (m, 2H), 2.15 (m, 2H), 2.55 (m, 4H), 2.8 (m, 2H), 3.5 (m, 2H), 3.6 (m, 4H), 3.9 (m, 2H), 4.3 (t, 2H), 5.1 (m, 1H), 6.2 (s, 2H), 6.9 (m, 2H), 7.8 (s, 1H), 8.45 (s, 1H); Mass Spectrum: $M+H^+$ 530 and 532, Elemental Analysis: Found C, 51.8; H, 5.8; N, 12.1; $C_{25}H_{28}ClN_5O_6$ $2.5H_2O$ requires C, 52.2; H, 5.8; N, 12.2%.

[20] The reactants were 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(3-chloropropoxy)-5-tetrahydropyran-4-yloxyquinazoline (described in Example 9 hereinafter) and morpholine. The required product was obtained in 30% yield and gave the following characterising data; NMR Spectrum: ($CDCl_3$ and CF_3CO_2D) 2.05 (m, 2H), 2.35 (m, 4H), 3.15 (m, 2H), 3.45 (m, 2H), 3.75 (m, 4H), 3.9 (m, 2H), 4.2 (m, 6H), 5.0 (m, 1H), 6.3 (s, 2H), 6.85 (s, 1H), 7.0 (s, 1H), 7.9 (s, 1H), 8.7 (s, 1H); Mass Spectrum: $M+H^+$ 544 and 546.

[21] The reactants were 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(3-chloropropoxy)-5-tetrahydropyran-4-yloxyquinazoline and 1-prop-2-ynylpiperazine. The reaction product was purified by column chromatography on a C18 reversed phase silica column (Waters Symmetry column, 5 microns silica, 19 mm diameter, 100 mm length) using a decreasingly polar mixture of water and acetonitrile (containing 1% acetic acid) as eluent. The organic solvents were evaporated and the pH of the aqueous phase was adjusted to 9. The solution was extracted with methylene chloride and the organic phase was dried over magnesium sulphate and evaporated. The resultant residue was triturated under pentane to give the required product in 48% yield which gave the following characterising data, NMR Spectrum: ($DMSOd_6$ and CD_3CO_2D) 1.85 (m, 2H), 2.0 (m, 2H), 2.15 (m, 2H), 2.5-2.8 (br m, 10H), 3.15 (s, 1H), 3.3 (s, 2H), 3.55 (t, 2H), 3.9 (m, 2H), 4.2 (t, 2H), 5.05 (m, 1H), 6.2 (s, 2H), 6.85 (s, 1H), 6.9 (s, 1H), 7.8 (s, 1H), 8.45 (s, 1H); Mass Spectrum: $M+H^+$ 581 and 583.

[22] The reactants were 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline and piperazine. The required product was obtained in 30% yield and gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.55 (d, 6H), 2.6 (m, 4H), 2.85 (t, 2H), 2.95 (m, 4H), 4.25 (t, 2H), 4.85 (m, 1H), 6.15 (s, 2H), 6.55 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Mass Spectrum: $M+H^+$ 487 and 489; Elemental Analysis: Found C, 55.4; H, 5.5; N, 16.4; $C_{23}H_{27}ClN_6O_4$ $0.1Et_2O$ $0.6H_2O$ requires C, 55.65; H, 5.8; N, 16.6%.

[23] The reactants were 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline and 1-(2-hydroxyethyl)piperazine. The reaction mixture was heated to 85°C for 8 hours. The reaction product was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. The material so obtained was triturated under diethyl ether to give the required product in 67% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.5 (d, 6H), 2.5-2.7 (br m, 12H), 3.65 (t, 2H), 4.25 (t, 2H), 4.8 (m, 1H), 6.15 (s, 2H), 6.6 (s, 1H), 6.85 (s, 1H), 7.25 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Mass Spectrum: $M+H^+$ 531 and 533; Elemental Analysis: Found C, 55.4; H, 6.05; N, 15.2; $C_{25}H_{31}ClN_6O_5$ 0.1Et_2O 0.5H_2O requires C, 55.7; H, 6.1; N, 15.35%.

[24] The reactants were 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline and pyrrolidine. The reaction mixture was heated to 80°C for 4 hours. The reaction product was purified by column chromatography on a C18 reversed phase silica column (Waters Symmetry column, 5 microns silica, 19 mm diameter, 100 mm length) using a decreasingly polar mixture of water and acetonitrile (containing 1% acetic acid) as eluent. The organic solvents were evaporated and the pH of the aqueous phase was adjusted to 9. The solution was extracted with methylene chloride and the organic phase was dried over magnesium sulphate and evaporated. The resultant residue was triturated under pentane to give the required product in 62% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.55 (d, 6H), 1.85 (m, 4H), 2.6 (m, 4H), 2.95 (t, 2H), 4.25 (t, 2H), 4.85 (m, 1H), 6.15 (s, 2H), 6.6 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Mass Spectrum: $M+H^+$ 472 and 474; Elemental Analysis: Found C, 58.3; H, 5.4; N, 14.7; $C_{23}H_{26}ClN_5O_4$ requires C, 58.5; H, 5.55; N, 14.8%.

[25] Using the detailed conditions described in Note [24] immediately above, 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(2-chloroethoxy)-5-tetrahydropyran-4-yloxyquinazoline was reacted with piperidine to give the required product in 52% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.45 (m, 2H), 1.55 (d, 6H), 1.65 (m, 4H), 2.5 (m, 4H), 2.85 (t, 2H), 4.25 (t, 2H), 4.85 (m, 1H), 6.15 (s, 2H), 6.6 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Mass Spectrum: $M+H^+$ 486 and 488; Elemental Analysis: Found C, 59.3; H, 5.9; N, 14.4; $C_{24}H_{28}ClN_5O_4$ requires C, 59.3; H, 5 8; N, 14.4%.

[26] Using the detailed conditions described in Note [24] immediately above, 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(2-chloroethoxy)-5-tetrahydropyran-

4-yloxyquinazoline was reacted with morpholine to give the required product in 57% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.55 (d, 6H), 2 6 (m, 4H), 2.85 (t, 2H), 3.75 (m, 4H), 4.25 (t, 2H), 4.85 (m, 1H), 6.15 (s, 2H), 6.55 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Mass Spectrum: $M+H^+$ 488 and 490; Elemental Analysis: Found C, 56.6; H, 5.4; N, 14.2; $C_{23}H_{26}ClN_5O_5$ requires C, 56.6; H, 5.4, N, 14.35%.

[27] Using the detailed conditions described in Note [24] immediately above, 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(2-chloroethoxy)-5-tetrahydropyran-4-yloxyquinazoline was reacted with 1-prop-2-ynylpiperazine to give the required product in 41% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.55 (d, 6H), 2.25 (s, 1H), 2.65 (br m, 8H), 2.9 (t, 2H), 3.3 (s, 2H), 4.25 (t, 2H), 4.85 (m, 1H), 6.15 (s, 2H), 6.55 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Mass Spectrum: $M+H^+$ 525 and 527; Elemental Analysis: Found C, 59.3; H, 5.4; N, 15.85; $C_{26}H_{29}ClN_6O_4$ requires C, 59.5; H, 5.6; N, 16.0%.

[28] The reactants were 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline and (3RS,4SR)-3,4-dimethoxypyrrolidine The required product was obtained in 78% yield and gave the following characterising data; NMR Spectrum: (DMSOd_6 and CD_3CO_2D) 1.45 (d, 6H), 2.7 (m, 2H), 3.0 (m, 2H), 3.15 (m, 2H), 3.3 (s, 6H), 3.75 (m, 2H), 4.25 (t, 2H), 5.5 (m, 1H), 6.2 (s, 2H), 6.8 (s, 1H), 6.85 (s, 1H), 7.8 (s, 1H), 8.45 (s, 1H), Mass Spectrum: $M+H^+$ 532 and 534; Elemental Analysis: Found C, 56.0; H, 5.6; N, 12.85; $C_{25}H_{30}ClN_5O_6$ 0.3H_2O requires C, 56.25; H, 5.7; N, 13.1%.

The (3RS,4SR)-3,4-dimethoxypyrrolidine used as a starting material was obtained as follows :-

A solution of tert-butyl (3RS,4SR)-3,4-dihydroxypyrrolidine-1-carboxylate (1 g) in DMF (20 ml) was cooled to 0-5°C and sodium hydride (60% dispersion in mineral oil, 0.433 g) was added portionwise. The reaction mixture was stirred at 5°C for 1 hour. Methyl iodide (0.675 ml) was added and the reaction mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The DMF was evaporated and the residue was partitioned between diethyl ether and water. The organic phase was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent. There was thus obtained tert-butyl (3RS,4SR)-3,4-dimethoxypyrrolidine-1-carboxylate as an oil (1.06 g);NMR Spectrum: ($CDCl_3$) 1.45 (s, 9H), 3.35 (m, 1H), 3 45 (s, 6H), 3.5 (m, 2H), 3.55 (m, 1H), 3 85 (m, 2H).

A cooled 5M solution of hydrogen chloride in isopropanol (3 ml) was added to a solution of tert-butyl (3RS,4SR)-3,4-dimethoxypyrrolidine-1-carboxylate (1 g) in methylene chloride (25 ml) that was cooled in an ice bath. The reaction mixture was allowed to warm to ambient temperature and was stirred for 16 hours. The solvent was evaporated. There was thus obtained (3RS,4SR)-3,4-dimethoxypyrrolidine hydrochloride as an oil (0.72 g); NMR Spectrum: ($DMSOd_6$) 3.1 (m, 2H), 3.25 (m, 2H), 3.35 (s, 6H), 4.0 (m, 2H), 9.3 (br s, 1H), 9.5 (br s, 1H).

The material so obtained was dissolved in methylene chloride and a 7M methanolic ammonia solution (0.2 ml) was added. The resultant mixture was stirred at ambient temperature for 5 minutes. The mixture was filtered and the solvent was evaporated at ambient temperature under vacuum. There was thus obtained (3RS,4SR)-3,4-dimethoxypyrrolidine which was used without any additional purification.

[29] Using the detailed conditions described in Note [24] immediately above except that the product was triturated under diethyl ether rather than under pentane, 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(2-chloroethoxy)-5-tetrahydropyran-4-yloxyquinazoline was reacted with (3RS,4SR)-3,4-ethylidenedioxypyrrolidine to give the required product in 67% yield which gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.45 (d, 3H), 1.55 (d, 6H), 2.3 (d, 2H), 2.95 (m, 2H), 3.25 (d, 2H), 4.25 (t, 2H), 4.55 (m, 2H), 4.8 (m, 1H), 5.0 (m, 1H), 6.15 (s, 2H), 6.55 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Mass Spectrum: $M+H^+$ 530 and 532; Elemental Analysis: Found C, 56.7; H, 5.5; N, 12.9; $C_{25}H_{28}ClN_5O_6$ $0.1Et_2O$ requires C, 56.8; H, 5.4; N, 13.0%.

The (3RS,4SR)-3,4-ethylidenedioxypyrrolidine used as a starting material was obtained as follows :-

A solution of tert-butyl (3RS,4SR)-3,4-dihydroxypyrrolidine-1-carboxylate (0.5 g) in methylene chloride (15 ml) was cooled to 0-5°C and acetaldehyde dimethylacetal (0.782 ml) and 4-toluenesulphonic acid (0.025 g) were added in turn. The reaction mixture was stirred at ambient temperature for 2 hours. The resultant mixture was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of petroleum ether (b.p. 40-60°C) and ethyl acetate as eluent There was thus obtained tert-butyl (3RS,4SR)-3,4-ethylidenedioxypyrrolidine-1-carboxylate as an oil (0.484 g);NMR Spectrum: ($CDCl_3$) 1 4 (d, 3H), 1.45 (s, 9H), 3.3 (m, 2H), 3.8 (m, 2H), 4.6 (m, 2H), 5.0 (q, 1H).

A cooled 5M solution of hydrogen chloride in isopropanol (4 ml) was added to a solution of tert-butyl (3RS,4SR)-3,4-ethylidenedioxypyrrolidine-1-carboxylate (0.475 g) in

methylene chloride (25 ml) that was cooled in an ice bath. The reaction mixture was allowed to warm to ambient temperature and was stirred for 2 hours. The solvent was evaporated and the residue was triturated under diethyl ether. The precipitate was collected by filtration, washed with diethyl ether and dried. There was thus obtained (3RS,4SR)-3,4-ethylidenedioxypyrrolidine hydrochloride (0.28 g); NMR Spectrum: (DMSOd_6 and CD_3CO_2D) 1.35 (d, 3H), 3.1 (d, 2H), 3.4 (d, 2H), 4.75 (s, 2H), 4.9 (q, 1H).

The material so obtained was dissolved in methylene chloride and a 7M methanolic ammonia solution (0.2 ml) was added. The resultant mixture was stirred at ambient temperature for 5 minutes. The mixture was filtered and the solvent was evaporated at ambient temperature under vacuum. There was thus obtained (3RS,4SR)-3,4-ethylidenedioxypyrrolidine which was used without any additional purification.

[30] The reactants were 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)quinazoline and 1-methylpiperazine. The required product was obtained in 74% yield and gave the following characterising data; NMR Spectrum: ($CDCl_3$ and CD_3CO_2D) ; Mass Spectrum: $M+H^+$ 501 and 503; Elemental Analysis: Found C, 57.5; H, 6 5; N, 16 0; $C_{24}H_{29}ClN_6O_4$ 0.23H_2O requires C, 57.8; H, 6.1; N, 16.2%.

[31] The reactants were 7-(3-chloropropoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline (the preparation of which is described in Example 12 hereinafter) and morpholine. The required product was obtained in 39% yield and gave the following characterising data; NMR Spectrum: ($CDCl_3$) 1.55 (d, 6H), 2.05 (m, 2H), 2.45 (m, 4H), 2.55 (t, 2H), 3.7 (m, 4H), 4.15 (t, 2H), 4.85 (m, 1H), 6.15 (s, 2H), 6.5 (s, 1H), 6 85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Mass Spectrum: $M+H^+$ 502 and 504; Elemental Analysis: Found C, 57.3; H, 5.65; N, 13.6; $C_{24}H_{28}ClN_5O_5$ requires C, 57.4; H, 5.6; N, 13.95%.

[32] The reactants were 7-(3-chloropropoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)quinazoline (the preparation of which is described in Example 13 hereinafter) and morpholine. The required product was obtained in 45% yield and gave the following characterising data; NMR Spectrum: (DMSOd_6 and CF_3CO_2D) 2.3 (m, 2H), 3.15 (m, 2H), 3.35 (m, 2H), 3.5 (m, 2H), 3.7 (m, 2H), 4.05 (m, 2H), 4.35 (m, 2H), 6.3 (s, 2H), 7.35 (s, 1H), 7.6 (d, 1H), 7.9 (s, 1H), 8.7 (d, 1H), 9.05 (s, 1H), Mass Spectrum: $M+H^+$ 444 and 446; Elemental Analysis: Found C, 57.0; H, 5.1; N, 15.7; $C_{21}H_{22}ClN_5O_4$ requires C, 56.8; H, 5.0; N, 15.8%.

[33] The reactants were 7-(3-chloropropoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)quinazoline and 1-acetylpiperazine. The required product was obtained in 34% yield and gave the following characterising data; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.05 (s, 3H), 2.3 (s, 2H), 3.0 (m, 2H), 3.15 (m, 1H), 3.3-3.4 (m, 4H), 3.6 (m, 2H), 4.05 (m, 1H), 4.35 (m, 2H), 4.5 (m, 1H), 6.3 (s, 2H), 7.35 (s, 1H), 7.6 (d, 1H), 7.9 (s, 1H), 8.7 (d, 1H), 9.0 (s, 1H); Mass Spectrum: $M+H^+$ 485 and 487; Elemental Analysis: Found C, 56.9; H, 5.4; N, 16.6; $C_{23}H_{25}ClN_6O_4$ $0.15Et_2O$ requires C, 57.1; H, 5.4; N, 16.9%.

[34] The reactants were 7-(2-chloroethoxy)-4-(2,3-methylenedioxypyrid-4-ylamino)quinazoline (the preparation of which is described in Example 14 hereinafter) and 1-prop-2-ynylpiperazine. After cooling of the reaction mixture and evaporation of the solvent, the residue was triturated under water and the resultant precipitate was isolated, washed with water and diethyl ether and dried. The required product was obtained in 60% yield and gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.26 (s, 1H), 2.8-2.6 (m, 8H), 2.97 (t, 2H), 3.3 (s, 2H), 4.03 (s, 3H), 4.33 (t, 2H), 6.14 (s, 2H), 6.98 (s, 1H), 7.12 (br s, 1H), 7.30 (s, 1H), 7.73 (d, 1H), 8.08 (d, 1H), 8.76 (s, 1H); Mass Spectrum: $M+H^+$ 463.

[35] The reactants were 7-(3-chloropropoxy)-4-(2,3-methylenedioxypyrid-4-ylamino)quinazoline (the preparation of which is described in Example 15 hereinafter) and 1-prop-2-ynylpiperazine. The required product was obtained in 57% yield and gave the following characterising data; NMR Spectrum: ($CDCl_3$) 2.13 (m, 2H), 2.26 (s, 1H), 2.6 (m, 10H), 3.31 (s, 2H), 4 04 (s, 3H), 4.26 (t, 2H), 6.14 (s, 2H), 6.98 (s, 1H), 7.12 (br s, 1H), 7.31 (s, 1H), 7.72 (d, 1H), 8.08 (d, 1H), 8.76 (s, 1H); Mass Spectrum: $M+H^+$ 477.

Example 7

6-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-methoxyquinazoline

Using an analogous procedure to that described in Example 1, 4-chloro-6-(2-chloroethoxy)-7-methoxyquinazoline was reacted with 4-amino-5-chloro-2,3-methylenedioxypyridine to give the title compound in 59% yield; NMR Spectrum: ($CDCl_3$) 3.95 (t, 2H), 4.05 (s, 3H), 4.4 (t, 2H), 6.1 (s, 2H), 7.05 (s, 1H), 7.2 (s, 1H), 7.35 (s, 1H), 7.75 (s, 1H), 8.75 (s, 1H); Mass Spectrum: $M+H^+$ 409 and 411.

The 4-chloro-6-(2-chloroethoxy)-7-methoxyquinazoline used as a starting material was prepared as follows :-

A mixture of 6-acetoxy-7-methoxy-3,4-dihydroquinazolin-4-one (International Patent Application WO 96/15118, Example 39 thereof; 8 g), thionyl chloride (80 ml) and DMF (0.8 ml) was stirred and heated to 80°C for 1.5 hours. The mixture was cooled to ambient temperature and the thionyl chloride was evaporated. The material so obtained was suspended in toluene and evaporated to dryness (twice). The resultant residue was diluted with methylene chloride (5 ml) and a 10:1 mixture (290 ml) of methanol and a saturated aqueous ammonium hydroxide solution was added. The resultant mixture was stirred and heated to 80°C for 5 minutes. The solvent was evaporated and the solid residue was suspended in water. The basicity of the mixture was adjusted to pH7 by the addition of dilute aqueous hydrochloric acid solution. The resultant solid was collected by filtration, washed with water and dried under vacuum over phosphorus pentoxide. There was thus obtained 4-chloro-6-hydroxy-7-methoxyquinazoline (6.08 g) which was used without further purification; NMR Spectrum: ($DMSOd_6$) 4.05 (s, 3H), 7.4 (s, 1H), 7.45 (s, 1H), 8.8 (s, 1H).

Di-tert-butyl azodicarboxylate (1.53 ml) was added portionwise over a few minutes to a stirred mixture of 4-chloro-6-hydroxy-7-methoxyquinazoline (1 g), 2-chloroethanol (0.382 ml), triphenylphosphine (1.74 g) and methylene chloride (30 ml) and the reaction mixture was stirred at ambient temperature for 2 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. There was thus obtained 4-chloro-6-(2-chloroethoxy)-7-methoxyquinazoline as a white solid (1.06 g); NMR Spectrum: ($CDCl_3$) 3.95 (t, 2H), 4.05 (s, 3H), 4.45 (t, 2H), 7.35 (s, 1H), 7.4 (s, 1H), 8.9 (s, 1H).

Example 8

6-(3-chloropropoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-methoxyquinazoline

Using an analogous procedure to that described in Example 1, 4-chloro-6-(3-chloropropoxy)-7-methoxyquinazoline was reacted with 4-amino-5-chloro-2,3-methylenedioxypyridine to give the title compound in 58% yield; NMR Spectrum: ($CDCl_3$) 2.4 (m, 2H), 3.8 (t, 2H), 4.05 (s, 3H), 4.35 (t, 2H), 6.15 (s, 2H), 7.05 (s, 1H), 7.2 (s, 1H), 7.3 (s, 1H), 7.75 (s, 1H), 8.7 (s, 1H); Mass Spectrum: $M+H^+$ 423 and 425.

The 4-chloro-6-(3-chloropropoxy)-7-methoxyquinazoline used as a starting material was prepared as follows :-

Di-tert-butyl azodicarboxylate (1.84 g) was added portionwise over a few minutes to a stirred mixture of 4-chloro-6-hydroxy-7-methoxyquinazoline (1.2 g), 3-chloropropanol (0.572 ml), triphenylphosphine (2.1 g) and methylene chloride (30 ml) and the reaction mixture was stirred at ambient temperature for 3 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and ethyl acetate as eluent. The material so obtained was triturated under diethyl ether. The resultant solid was isolated and dried under vacuum. There was thus obtained 4-chloro-6-(3-chloropropoxy)-7-methoxyquinazoline as a white solid (0.84 g); NMR Spectrum: ($CDCl_3$) 2.4 (m, 2H), 3.8 (t, 2H), 4.05 (s, 3H), 4.35 (t, 2H), 7.35 (s, 1H), 7.45 (s, 1H), 8.9 (s, 1H).

Example 9

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(3-chloropropoxy)-5-tetrahydropyran-4-yloxyquinazoline

Using an analogous procedure to that described in Example 1, 4-chloro-7-(3-chloropropoxy)-5-tetrahydropyran-4-yloxyquinazoline was reacted with 4-amino-5-chloro-2,3-methylenedioxypyridine to give the title compound in 78% yield; Mass Spectrum: $M+H^+$ 493 and 495.

The 4-chloro-7-(3-chloropropoxy)-5-tetrahydropyran-4-yloxyquinazoline used as a starting material was prepared as follows :-

Using an analogous procedure to that described in the portion of Example 4 that is concerned with the preparation of starting materials, 4-chloro-7-hydroxy-5-tetrahydropyran-4-yloxyquinazoline (2.5 g) was reacted with 3-chloropropanol. There was thus obtained the required starting material in 21% yield; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 1.7 (m, 2H), 2.0 (m, 2H), 2.25 (m, 2H), 3.55 (m, 2H), 3.8 (t, 2H), 3.9 (m, 2H), 4.3 (t, 2H), 4.95 (m, 1H), 6.8 (s, 1H), 6.9 (s, 1H), 9.2 (s, 1H).

Example 10

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(2,4-dimethoxybenzyloxy)-5-isopropoxyquinazoline

Using an analogous procedure to that described in Example 1, 4-chloro-7-(2,4-dimethoxybenzyloxy)-5-isopropoxyquinazoline was reacted with 4-amino-5-chloro-2,3-methylenedioxypyridine to give the title compound in 75% yield; NMR

Spectrum: ($CDCl_3$) 1.55 (d, 6H), 3.8 (s, 3H), 3.85 (s, 3H), 4.8 (m, 1H), 5.15 (s, 2H), 6.15 (s, 2H), 6.5 (m, 2H), 6.6 (s, 1H), 7.0 (s, 1H), 7.35 (d, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Mass Spectrum: $M+H^+$ 525 and 527.

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

Sodium hydride (60% dispersion in mineral oil; 40 g) was added portionwise to a solution of isopropanol (30 g) in DMF (500 ml) that had been cooled to 5°C. The mixture was allowed to warm to ambient temperature and was stirred for 60 minutes. 5,7-Difluoro-3,4-dihydroquinazolin-4-one (International Patent Application WO 01/94341; 90 g) was added and the mixture was stirred at ambient temperature for 3 hours. The mixture was poured into water (1 litre) and, with vigorous stirring, glacial acetic acid was added to acidify the mixture to pH5. The resultant solid was isolated, washed with water and with diethyl ether and dried under vacuum. There was thus obtained 7-fluoro-5-isopropoxy-3,4-dihydroquinazolin-4-one (79 g); NMR Spectrum: ($DMSOd_6$) 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 (61 g), 2,4-dimethoxybenzyl alcohol (138 g), potassium tert-butoxide (185 g) and THF (1 5 litres) was stirred and heated to reflux for 18 hours. After cooling, the solvent was evaporated and a mixture of methylene chloride (400 ml) and water (600 ml) was added. With cooling, the 2-phase mixture was neutralised by the addition of 2N aqueous hydrochloric acid. The mixture was filtered and the organic phase was separated, dried over magnesium sulphate and evaporated. The residue was triturated under diethyl ether. There was thus obtained 7-(2,4-dimethoxybenzyloxy)-5-isopropoxy-3,4-dihydroquinazolin-4-one (68 g); NMR Spectrum: ($DMSOd_6$) 1.28 (s, 6H), 3.78 (s, 3H), 3.82 (s, 3H), 4.63 (m, 1H), 5.06 (s, 2H), 6.55 (m, 2H), 6.62 (s, 1H), 6.71 (s, 1H), 7.33 (d, 1H), 7.88 (s, 1H); Mass Spectrum: $M+H^+$ 371

A mixture of a portion (4 g) of the material so obtained, phosphorus oxychloride (1 98 g), diisopropylethylamine (3.6 g) and methylene chloride (100 ml) was stirred and heated to 75°C for 3 hours The mixture was cooled and evaporated. The residue was dried under vacuum for 1 hour and purified by column chromatography on silica using a 20:3 mixture of methylene chloride and ethyl acetate as eluent. There was thus obtained 4-chloro-7-(2,4-dimethoxybenzyloxy)-5 isopropoxyquinazoline as a solid (2.63 g); NMR Spectrum: ($CDCl_3$) 1.46 (s, 3H), 1.47 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 4.68 (m, 1H), 5.16 (s, 2H), 6.52 (m, 2H), 6.65 (s, 1H), 7.06 (s, 1H), 7 33 (d, 1H), 8.78 (s, 1H); Mass Spectrum: $M+H^+$ 389.

Example 11

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-hydroxy-5-isopropoxyquinazoline

Trifluoroacetic acid (4.5 ml) was added to a solution of 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(2,4-dimethoxybenzyloxy)-5-isopropoxyquinazoline (0.53 g) in methylene chloride (9 ml) and the reaction mixture was stirred at ambient temperature for 30 minutes. The solvents were evaporated to give the di-trifluoroacetic acid salt (0.618 g) of the required compound. A portion of this salt was dissolved in methylene chloride (2 ml) and a 7M methanolic ammonia solution was added. The mixture was filtered and the filtrate was evaporated. There was thus obtained the title compound; Mass Spectrum: $M+H^+$ 375 and 377.

Example 12

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(3-chloropropoxy)-5-isopropoxyquinazoline

A mixture of 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-hydroxy-5-isopropoxyquinazoline di-trifluoroacetic acid salt (0.615 g), 1,3-dichloropropane (0.38 ml), potassium carbonate (0.56 g) and DMF (6 ml) was stirred and heated to 80°C for 5 hours. After cooling, the solids were filtered off and the filtrate was evaporated. The residue was purified by column chromatography on silica using a 24:1 mixture of methylene chloride and methanol as eluent. There was thus obtained the title compound (0.32 g); NMR Spectrum: ($CDCl_3$) 1.55 (d, 6H), 2.3 (m, 2H), 3.8 (t, 2H), 4.25 (t, 2H), 4.9 (m, 1H), 6.15 (s, 2H), 6.5 (s, 1H), 6.9 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H).

Example 13

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(3-chloropropoxy)quinazoline

Using an analogous procedure to that described in Example 1, 4-chloro-7-(3-chloropropoxy)quinazoline was reacted with 4-amino-5-chloro-2,3-methylenedioxypyridine to give the title compound in 89% yield; NMR Spectrum: ($DMSOd_6$ and CF_3CO_2D) 2.25 (m, 2H), 3.8 (t, 2H), 4.35 (t, 2H), 6.25 (s, 2H), 7.35 (s, 1H), 7.6 (d, 1H), 7.9 (s, 1H), 8.7 (d, 1H), 9.0 (s, 1H).

The 4-chloro-7-(3-chloropropoxy)quinazoline used as a starting material was prepared as follows :-

Sodium hydride (60% dispersion in mineral oil; 2.92 g) was added portionwise over 45 minutes to a stirred mixture of 1,3-propanediol (5.3 ml) and DMF (20 ml) that had been cooled to 0°C. The resultant mixture was stirred at ambient temperature for 1 hour and then heated to 60°C. 7-Fluoro-3,4-dihydroquinazolin-4-one (International Patent Application WO 01/04102, Example 2, Note [12] thereof; 2 g) was added and the reaction mixture was stirred and heated to 115°C for 3.5 hours. The reaction mixture was cooled to 0°C and water (50 ml) was added. The mixture was acidified to pH5.9 with 2N aqueous hydrochloric acid. The resultant precipitate was collected by filtration, washed with water and dried under vacuum over phosphorus pentoxide at 40°C. The solid so obtained was washed with diethyl ether and dried again under vacuum. There was thus obtained 7-(3-hydroxypropoxy)-3,4-dihydroquinazolin-4-one (2.1 g); NMR Spectrum. ($DMSOd_6$) 1.9 (m, 2H), 3.6 (m, 2H), 4.15 (m, 2H), 4.6 (br s, 2H), 7.1 (m, 2H), 8.05 (m, 2H); Mass Spectrum: $M+H^+$ 221.

A mixture of 7-(3-hydroxypropoxy)-3,4-dihydroquinazolin-4-one (1 g), 1,2-dichloroethane (50 ml), triphenylphosphine (5.24 g) and carbon tetrachloride (2.9 ml) was stirred and heated to 70°C for 2 hours. The solvent was evaporated and the residue was purified by column chromatography on silica using initially methylene chloride followed by gradually increasing the polarity of the solvent up to a 9:1 mixture of methylene chloride and methanol as eluent There was thus obtained 4-chloro-7-(3-chloropropoxy)quinazoline (1.23 g; containing 0.6 mole of triphenylphosphine oxide per mole of product); Mass Spectrum: $M+H^+$ 393 and 395.

Example 14

7-(2-chloroethoxy)-4-(2,3-methylenedioxypyrid-4-ylamino)-6-methoxyquinazoline

Sodium hexamethyldisilazane (1M solution in THF; 2 ml) was added dropwise to a mixture of 4-amino-2,3-methylenedioxypyridine (0.138 g), 4-chloro-7-(2-chloroethoxy)-6-methoxyquinazoline (0.272 g) and THF (5 ml) that had been cooled to 0°C. The mixture was stirred at 0°C for 1 hour. The resultant mixture was allowed to warm to ambient temperature and was stirred for 2 hours. The reaction was quenched by the addition of glacial acetic acid (0.12 ml). The solvents were evaporated and the residue was partitioned between methylene chloride and an aqueous ammonium hydroxide solution. The organic layer was collected and concentrated to a small volume. Diethyl ether was added and a precipitate formed. The resultant solid was isolated, washed with diethyl ether and dried. There was thus obtained the title compound (0.245 g); NMR Spectrum: ($DMSOd_6$) 3.97 (s, 3H), 4.04 (m,

2H), 4.45 (m, 2H), 6.12 (s, 2H), 7.13 (br d, 1H), 7.25 (s, 1H), 7.60 (d, 1H), 7.83 (s, 1H), 8.47 (s, 1H), 9.87 (br s, 1H); Mass Spectrum: $M+H^+$ 375.

The 4-amino-2,3-methylenedioxypyridine used as a starting material was prepared as follows :-

Dibromomethane (31.5 ml) was added to a mixture 2,3-dihydroxypyridine (33 g), potassium carbonate (62 g) and NMP (200 ml) and the mixture was stirred and heated to 90°C for 16 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was partitioned between diethyl ether (5 x 100 ml) and water (200 ml). The organic extracts were combined and concentrated under vacuum to a volume of about 20 ml. Petroleum ether (b.p 40-60°C; 300 ml) was added and the solution was washed with brine. The organic layer was separated and evaporated. There was thus obtained 2,3-methylenedioxypyridine as a liquid (5.1 g); NMR Spectrum: ($CDCl_3$) 6.05 (s, 2H), 6.76 (m, 1H), 6.99 (d, 1H), 7.65 (d, 1H).

Using an analogous procedure to that described in the second paragraph of the portion of Example 1 that is concerned with the preparation of the starting material 4-amino-5-chloro-2,3-methylenedioxypyridine, 2,3-methylenedioxypyridine was reacted with carbon dioxide gas to give 2,3-methylenedioxypyridine-4-carboxylic acid in 80% yield; NMR Spectrum: ($DMSOd_6$) 6.24 (s, 2H), 7.13 (d, 1H); 7.63 (d, 1H).

Using an analogous procedure to that described in the third paragraph of that portion of Example 1 that is concerned with the preparation of starting materials, 2,3-methylenedioxypyridine-4-carboxylic acid was reacted with diphenylphosphoryl azide and anhydrous tert-butanol to give tert-butyl 2,3-methylenedioxypyrid-4-ylcarbamate in 62% yield; Mass Spectrum: $M+H^+$ 239

Using an analogous procedure to that described in the last paragraph of that portion of Example 1 that is concerned with the preparation of starting materials, tert-butyl 2,3-methylenedioxypyrid-4-ylcarbamate was reacted with trifluoroacetic acid to give 4-amino-2,3-methylenedioxypyridine in 80% yield; NMR Spectrum: ($CDCl_3$) 3.98 (m, 2H), 5 98 (s, 2H), 6.24 (d, 1H), 7.44 (d, 1H); Mass Spectrum: $M+H^+$ 139.

Example 15

7-(3-chloropropoxy)-4-(2,3-methylenedioxypyrid-4-ylamino)-6-methoxyquinazoline

Using an analogous procedure to that described in Example 14, 4-chloro-7-(3-chloropropoxy)-6-methoxyquinazoline was reacted with 4-amino-2,3-methylenedioxypyridine to give the title compound in 68% yield; NMR Spectrum:

52

(DMSOd_6) 2.26 (m, 2H), 3.83 (m, 2H), 3.96 (s, 3H), 4.28 (m, 2H), 6.12 (s, 2H), 7.15 (br d, 1H), 7.25 (s, 1H), 7.61 (d, 1H), 7.81 (s, 1H), 8.49 (s, 1H), 9.79 (br s, 1H); Mass Spectrum: $M+H^+$ 389.

Example 16

7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(2,3-methylenedioxypyrid-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline

Using an analogous procedure to that described in Example 1, 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-chloro-5-tetrahydropyran-4-yloxyquinazoline (0.113 g) was reacted with 4-amino-2,3-methylenedioxypyridine (0.036 g). The reaction mixture was quenched with glacial acetic acid (0.031 g) and diluted with methanol. The mixture was evaporated and the residue was purified by column chromatography on a C18 reversed phase silica column (Waters Symmetry column,5 microns silica, 20 mm diameter, 100 mm length) using a decreasingly polar mixture of water and acetonitrile (containing 1% acetic acid) as eluent. The material so obtained was diluted with a 7M methanolic ammonia solution. The mixture was evaporated and the material so obtained was dissolved in methylene chloride. The solution was dried over magnesium sulphate and evaporated to give the title compound as a foam in 53% yield; NMR Spectrum: ($CDCl_3$) 2.02 (m, 2H), 2.1 (s, 3H), 2.22 (m, 2H), 2.6 (m, 4H), 2.9 (m, 2H), 3.51 (m, 2H), 3.6 (m, 2H), 3.66 (m, 2H), 4.1 (m, 2H), 4.25 (m, 2H), 4.73 (m, 1H), 6.13 (s, 2H), 6 59 (s, 1H), 6.9 (s, 1H), 7.7 (d, 1H), 8.36 (d, 1H), 8.66 (s, 1H); Mass Spectrum: $M+H^+$ 537.

The 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-chloro-5-tetrahydropyran-4-yloxyquinazoline used as a starting material was prepared as follows :-

Sodium hydride (60% dispersion in mineral oil; 0.6 g) was added portionwise to a solution of 4-hydroxytetrahydropyran (0.78 g) in DMF (10 ml) that had been cooled to 5°C. The mixture was allowed to warm to ambient temperature and was stirred for 15 minutes. 5,7-Difluoro-3,4-dihydroquinazolin-4-one (International Patent Application WO 01/94341; 0.9 g) was added and the mixture was stirred at ambient temperature for 30 minutes. The mixture was poured into water (100 ml) and, with vigorous stirring, glacial acetic acid was added to acidify the mixture to pH5. The resultant solid was isolated, washed with water and with diethyl ether and dried under vacuum. There was thus obtained 7-fluoro-5-tetrahydropyran-4-yloxy-3,4-dihydroquinazolin-4-one (1.1 g); NMR Spectrum: (DMSOd_6)

1.6-1.75 (m, 2H), 1.9-2.0 (m, 2H), 3.5-3.6 (m, 2H), 3.85-3.95 (m, 2H), 4.8 (m, 1H), 6.9 (m, 1H), 7.05 (m, 1H), 8.0 (s, 1H); Mass Spectrum: $M+H^+$ 265.

After repetition of the prior reaction, a mixture of 7-fluoro-5-tetrahydropyran-4-yloxy-3,4-dihydroquinazolin-4-one (5.3 g), 2-piperazin-1-ylethanol (3.9 g), potassium tert-butoxide (6.7 g) and THF (200 ml) was stirred and heated to reflux for 3 hours. A second portion (6.7 g) of potassium tert-butoxide was added and the mixture was heated to reflux for a further 12 hours. The mixture was cooled to ambient temperature and filtered. The filtrate was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a 7M methanolic ammonia solution as eluent. The material so obtained was triturated under diethyl ether. There was thus obtained 7-(2-piperazin-1-ylethoxy)-5-tetrahydropyran-4-yloxy-3,4-dihydroquinazolin-4-one (5.2 g); NMR Spectrum: (DMSOd_6 and CF_3CO_2D) 1.75 (m, 2H), 2.03 (m, 2H), 3.2-4.0 (m, 14H), 4.59 (m, 2H), 4.92 (m, 1H), 6.88 (s, 1H), 6.9 (s, 1H), 9.28 (s, 1H); Mass Spectrum: $M+H^+$ 375.

Acetic anhydride (1.51 ml) was added dropwise to a stirred mixture of 7-(2-piperazin-1-ylethoxy)-5-tetrahydropyran-4-yloxy-3,4-dihydroquinazolin-4-one (5 g) and water (20 ml) and the resultant mixture was stirred at ambient temperature for 10 minutes. The reaction mixture was evaporated and the residue was triturated under diethyl ether. The resultant solid was isolated, washed with diethyl ether and dried under vacuum. There was thus obtained 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxy-3,4-dihydroquinazolin-4-one (5.5 g); NMR Spectrum: (DMSOd_6 and CF_3CO_2D) 1.75 (m, 2H), 2 03 (m, 2H), 2.08 (s, 3H), 3.0-4.2 (m, 13H), 4 56 (m, 3H), 4.94 (m, 1H), 6.84 (s, 1H), 6.9 (s, 1H), 9.21 (s, 1H); Mass Spectrum: $M+H^+$ 417.

A mixture of a portion (0.416 g) of the material so obtained, triphenylphosphine (0.655 g), carbon tetrachloride (0.34 ml) and 1,2-dichloroethane (20 ml) was stirred and heated to 70°C for 1.5 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and a 7M methanolic ammonia solution (a solvent gradient having from 1% to 3% methanolic ammonia solution) as eluent. There was thus obtained 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-chloro-5-tetrahydropyran-4-yloxyquinazoline as a solid (0.35 g); NMR Spectrum: ($CDCl_3$) 2.0 (m, 2H), 2.1 (s, 3H), 2.12 (m, 2H), 2.58 (m, 4H), 2.9 (m, 2H), 3.51 (m, 2H), 3.68 (m, 4H), 4.05 (m, 2H), 4.25 (m, 2H), 4.75 (m, 1H), 6.62 (s, 1H), 6.94 (s, 1H), 8.82 (s, 1H); Mass Spectrum: $M+H^+$ 435 and 437.

53

Example 17

7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline

Using an analogous procedure to that described in Example 16, 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-chloro-5-isopropoxyquinazoline was reacted with 4-amino-2,3-methylenedioxypyridine to give the title compound in 55% yield; NMR Spectrum: ($CDCl_3$) 1.55 (s, 3H), 1.56 (s, 3H), 2.1 (s, 3H), 2.59 (m, 4H), 2.89 (m, 2H), 3.51 (m, 2H), 3.67 (m, 2H), 4.24 (m, 2H), 4.85 (m, 1H), 6 13 (s, 2H), 6.57 (s, 1H), 6.85 (s, 1H), 7.71 (d, 1H), 8.41 (d, 1H), 8.66 (s, 1H); Mass Spectrum: $M+H^+$ 495.

The 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-chloro-5-isopropoxyquinazoline that is required as a starting material was prepared as follows using analogous procedures to those described in the portion of Example 16 that is concerned with the preparation of starting materials.

5,7-Difluoro-3,4-dihydroquinazolin-4-one was reacted with isopropanol to give 7-fluoro-5-isopropoxy-3,4-dihydroquinazolin-4-one in 73% yield; NMR Spectrum: ($DMSOd_6$) 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.

The material so obtained was reacted with 2-piperazin-1-ylethanol to give 5-isopropoxy-7-(2-piperazin-1-ylethoxy)-3,4-dihydroquinazolin-4-one in 63% yield; NMR Spectrum: ($CDCl_3$) 1.45 (s, 3H), 1.46 (s, 3H), 2.4-3.0 (m, 10H), 4.2 (t, 2H), 4.62 (m, 1H), 6.51 (s, 1H), 6.72 (s, 1H), 7.9 (s, 1H).

The material so obtained was reacted with an excess of acetic anhydride but using methylene chloride rather than water as the reaction solvent. The reaction mixture was stirred at ambient temperature for 15 minutes. The mixture was partitioned between methylene chloride and a saturated aqueous sodium bicarbonate solution. The organic layer was washed with water and with brine, dried over magnesium sulphate and evaporated. The residue was triturated under a mixture of acetonitrile and diethyl ether. There was thus obtained 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-5-isopropoxy-3,4-dihydroquinazolin-4-one in 70% yield; NMR Spectrum: ($CDCl_3$) 1.46 (s, 3H), 1.47 (s, 3H), 2.1 (s, 3H), 2.58 (m, 4H), 2 87 (t, 2H), 3.5 (m, 2H), 3.66 (m, 2H), 4.21 (t, 2H), 4.63 (m, 1H), 6.51 (s, 1H), 6 72 (s, 1H), 7.9 (s, 1H), 9.9 (br s, 1H); Mass Spectrum: $M+H^+$ 375.

The material so obtained was reacted with carbon tetrachloride and triphenylphosphine to give 7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-chloro-5-isopropoxyquinazoline in 68% yield which was used without further purification.

Example 18

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[4-(2-dimethylaminoacetyl)piperazin-1-yl]ethoxy}-5-isopropoxyquinazoline

4-(5-Chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxy-7-(2-piperazin-1-ylethoxy)quinazoline (0.2 g) was added to a stirred mixture of 2-dimethylaminoacetyl chloride hydrochloride (0.097 g), triethylamine (0.15 ml) and methylene chloride (5 ml) that had been cooled to 0°C. The reaction mixture was allowed to warm to ambient temperature and stirred for 2 hours. A second portion of each of 2-dimethylaminoacetyl chloride hydrochloride (0.097 g) and triethylamine (0.057 ml) were added and the reaction was stirred at ambient temperature for 16 hours overnight. Methylene chloride (50 ml) was added and the reaction mixture was extracted twice with a saturated aqueous sodium bicarbonate solution. The organic phase was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar solvent mixtures, starting with a 9:1 mixture of methylene chloride and methanol and ending with a 90:8:2 mixture of methylene chloride, methanol and a saturated methanolic ammonia solution. There was thus obtained the title compound as a foam (0.155 g); NMR Spectrum: ($CDCl_3$) 1.55 (d, 6H), 2.3 (s, 6H), 2.6 (m, 4H), 2.9 (t, 2H), 3.1 (s, 2H), 3.65 (m, 4H), 4.25 (t, 2H), 4.85 (s, 1H), 6.15 (s, 2H), 6.55 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Mass Spectrum: $M+H^+$ 572 and 574, Elemental Analysis: Found C, 55.1; H, 6.1; N, 16.8; $C_{27}H_{34}ClN_7O_5$ $0.75H_2O$ requires C, 55.4; H, 6.1; N, 16.7%.

Example 19

7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxyquinazoline

Using a similar procedure to that described in Example 1, a solution of 4-amino-5-chloro-2,3-methylenedioxypyridine (0.193 g) in DMF (2 ml) was added to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 0.048 g) in DMF (2 ml) and the mixture was stirred at ambient temperature for 15 minutes. A solution of 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-4-chloro-6-methoxyquinazoline

[International Patent Application WO 02/16352 (Note [24] within Example 2 thereof; 0.38 g] in DMF (4 ml) was added and the resultant mixture was stirred at ambient temperature for 1 hour. The reaction mixture was partitioned between ethyl acetate and brine. The organic phase was dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using a 49:1 mixture of methylene chloride and methanol. There was thus obtained the title compound as a solid (0.24 g); NMR Spectrum: ($DMSOd_6$) 1.29 (m, 2H), 1.45 (s, 9H), 1.8 (m, 2H), 2.04 (m, 1H), 2.83 (m, 2H), 4.0 (m, 7H), 8.12 (br s, 2H), 7.17 (br s, 1H), 7.72 (m, 2H), 8.37 (br s, 1H), 9.37 (br s, 1H); Mass Spectrum: $M+H^+$ 544 and 546:

Example 20

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazoline

Trifluoroacetic acid (1 ml) was added to a solution of 7-(N-tert-butoxycarbonylpiperidin-4-ylmethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxyquinazoline (0.253 g) in methylene chloride (10 ml) and the reaction mixture was stirred at ambient temperature for 1 hour. The reaction mixture was evaporated. Toluene was added to the residue and the mixture was evaporated. The residue was purified by column chromatography on silica (Isolute SCX column) using a 7M methanolic ammonia solution as eluent. There was thus obtained the title compound as a solid (0.187 g); NMR Spectrum: ($DMSOd_6$) 1.25 (m, 2H), 1.75 (d, 2H), 1.93 (m, 1H), 2.54 (m, 2H), 3.0 (d, 2H), 3.93 (s, 3H), 3.98 (d, 2H), 6.17 (s, 2H), 7.15 (s, 1H), 7.76 (s, 1H), 7.78 (s, 1H), 8.23 (s, 1H); Mass Spectrum: $M+H^+$ 444 and 446.

Example 21

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-[N-(2-dimethylaminoacetyl)piperidin-4-ylmethoxy]-6-methoxyquinazoline

Diisopropylethylamine (0.118 ml) was added to a mixture of 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxy-7-(piperidin-4-ylmethoxy)quinazoline (0.15 g), N,N-dimethylglycine (0.042 g), 2-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate(V) (0.154 g) and DMF (3 ml) and the reaction mixture was stirred at ambient temperature for 16 hours. The mixture was diluted with ethyl acetate and washed with brine. The organic solution was dried over magnesium

sulphate and evaporated. The residue was purified by column chromatography on silica using a 100:3 mixture of methylene chloride and a 7M methanolic ammonia solution as eluent. There was thus obtained the title compound as a solid (0.051 g); NMR Spectrum: ($DMSOd_6$) 1.11-1.36 (m, 2H), 1.83 (d, 2H), 2.11 (m, 1H), 2.19 (s, 6H), 2.61 (t, 1H), 3.03 (m, 2H), 3.12 (d, 1H), 3.93 (s, 3H), 4.06 (m, 3H), 4.4 (d, 1H), 6.19 (br s, 2H), 7.19 (br s, 1H), 7.78 (m, 2H), 8.39 (br s, 1H), 9.71 (br s, 1H); Mass Spectrum: $M+H^+$ 529 and 531.

Example 22

7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline

A mixture of 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline (24 g), 1-acetylpiperazine (21 g), potassium iodide (18 g) and DMA (500 ml) was stirred and heated to 100°C for 4 hours. The solvent was evaporated and the residue was partitioned between methylene chloride (1 litre) and water (500 ml). The aqueous layer was extracted with methylene chloride. The organic solutions were combined, washed with brine, dried over magnesium sulphate and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol (from a 20:1 mixture to a 10:1 mixture) as eluent. After evaporation of the solvent, the material so obtained was triturated under diethyl ether. There was thus obtained the title compound as a white solid (26.2 g); m.p. 208-210°C.

The 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline used as a starting material was obtained as follows :-

Sodium hexamethyldisilazane (1M solution in THF, 164 ml) was added dropwise over one hour to a ice-cooled mixture of 4-chloro-7-(2,4-dimethoxybenzyloxy)-5-isopropoxyquinazoline (32 g), 4-amino-5-chloro-2,3-methylenedioxypyridine (15.6 g) and THF (430 ml) whilst maintaining the temperature of the reaction mixture at about 3°C. At the end of the addition, the reaction mixture was allowed to warm to ambient temperature and was stirred for 2.5 hours. The reaction mixture was cooled to 0°C and a mixture of acetic acid (9.4 ml) and water (250 ml) was added. The mixture was evaporated and the residue was partitioned between methylene chloride and water, the basicity of the aqueous phase having been adjusted to 7.5 by the addition of 3N aqueous hydrochloric acid solution. The organic phase was separated and the aqueous phase was extracted three times with methylene chloride. The organic layers were combined, washed with brine, dried over magnesium

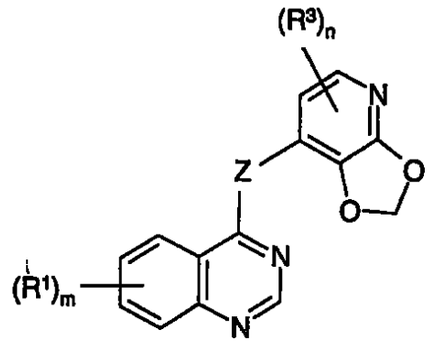
sulphate and evaporated. The resultant solid was triturated under ethyl acetate. There was thus obtained 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(2,4-dimethoxybenzyloxy)-5-isopropoxyquinazoline as a white solid (38 g); Mass Spectrum: $M+H^+$ 525 and 527.

Triethylsilane (70 ml) and trifluoroacetic acid (48 ml) were added in turn to an ice-cooled solution of 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(2,4-dimethoxybenzyloxy)-5-isopropoxyquinazoline (37.7 g) in methylene chloride (560 ml) and the resultant reaction mixture was stirred at ambient temperature for 1 hour. The solvents were evaporated under high vacuum. The resultant solid was triturated under ethyl acetate. The material so obtained was isolated, washed with ethyl acetate and dried under high vacuum There was thus obtained the di-trifluoroacetic acid salt (37.4 g) of 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-hydroxy-5-isopropoxyquinazoline which was used without further purification.

Potassium carbonate (34.6 g) was added to a mixture of 4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-hydroxy-5-isopropoxyquinazoline di-trifluoroacetic acid salt (49 g), 1,2-dichloroethane (440 ml) and DMF (245 ml) and the mixture was stirred and heated to 90°C for 3.5 hours. An additional portion (7 g) of potassium carbonate was added and the mixture was stirred at 90°C for a further hour. The reaction mixture was cooled to ambient temperature and the solids were filtered off and washed with methylene chloride. The filtrate and washings were combined and evaporated. The resultant residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol (from a 50:1 mixture to a 20:1 mixture) as eluent. There was thus obtained 7-(2-chloroethoxy)-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline as a white solid (37.1 g); Mass Spectrum: $M+H^+$ 437 and 439.

CLAIMS

1. A quinazoline derivative of the Formula I



I

wherein Z is an O, S, SO, SO_2, $N(R^2)$ or $C(R^2)_2$ group wherein each R^2 group, which may be the same or different, is hydrogen or (1-8C)alkyl;

m is 0, 1, 2 or 3;

each R^1 group, which may be the same or different, is selected from halogeno, trifluoromethyl, cyano, isocyano, nitro, hydroxy, mercapto, amino, formyl, carboxy, carbamoyl, (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 :

$$Q^1\text{-}X^1\text{-}$$

wherein X^1 is a direct bond or is selected from O, S, SO, SO_2, $N(R^4)$, CO, $CH(OR^4)$, $CON(R^4)$, $N(R^4)CO$, $SO_2N(R^4)$, $N(R^4)SO_2$, $OC(R^4)_2$, $SC(R^4)_2$ and $N(R^4)C(R^4)_2$, wherein R^4 is hydrogen or (1-8C)alkyl, and Q^1 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)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 R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, S, SO, SO_2, $N(R^5)$, CO, $CH(OR^5)$, $CON(R^5)$, $N(R^5)CO$, $SO_2N(R^5)$, $N(R^5)SO_2$, CH=CH and C≡C wherein

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

and wherein any CH_2=CH- or HC≡C- group within a R^1 substituent optionally bears at the terminal CH_2= 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 :

$$Q^2-X^2-$$

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

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more halogeno or (1-8C)alkyl substituents or a substituent selected from hydroxy, cyano, amino, carboxy, carbamoyl, oxo, thioxo, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino and N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, or from a group of the formula :

$$-X^3-Q^3$$

wherein X^3 is a direct bond or is selected from O, S, SO, SO_2, $N(R^7)$, CO, $CH(OR^7)$, $CON(R^7)$, $N(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, $C(R^7)_2O$, $C(R^7)_2S$ and $N(R^7)C(R^7)_2$, wherein R^7 is hydrogen or (1-8C)alkyl, and Q^3 is aryl, aryl-(1-6C)alkyl, (3-7C)cycloalkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl,

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

N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, (2-6C)alkanoyloxy, (2-6C)alkanoylamino, N-(1-6C)alkyl-(2-6C)alkanoylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, (1-6C)alkanesulphonylamino, N-(1-6C)alkyl-(1-6C)alkanesulphonylamino and (1-3C)alkylenedioxy, or from a group of the formula :

$$-X^4-R^8$$

wherein X^4 is a direct bond or is selected from O and $N(R^9)$, wherein R^9 is hydrogen or (1-8C)alkyl, and R^8 is halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, (2-6C)alkanoylamino-(1-6C)alkyl or (1-6C)alkoxycarbonylamino-(1-6C)alkyl, or from a group of the formula :

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

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

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

n is 0, 1, 2 or 3; and

each R^3 group, which may be the same or different, is 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, (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 :

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

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

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

$$-X^7-Q^5$$

wherein X^7 is a direct bond or is selected from O, S, SO, SO_2, $N(R^{13})$, CO, $CH(OR^{13})$, $CON(R^{13})$, $N(R^{13})CO$, $SO_2N(R^{13})$, $N(R^{13})SO_2$, $C(R^{13})_2O$, $C(R^{13})_2S$ and $N(R^{13})C(R^{13})_2$, wherein R^{13} is hydrogen or (1-8C)alkyl, and Q^5 is aryl, aryl-(1-6C)alkyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl or heterocyclyl-(1-6C)alkyl which optionally bears 1 or 2 substituents, which may be the same or different. selected from halogeno, (1-8C)alkyl, (2-8C)alkenyl, (2-8C)alkynyl and (1-6C)alkoxy, and any heterocyclyl group within Q^5 optionally bears 1 or 2 oxo or thioxo substituents;
or a pharmaceutically-acceptable salt thereof.

2. A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 wherein Z is NH.

3. A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 wherein
m is 1 and the R^1 group is located at the 5-, 6- or 7-position or m is 2 and the R^1 groups, which may be the same or different, are located at the 5- and 7-positions or at the 6- and 7-positions and each R^1 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 R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(Me), CH=CH and C≡C,

and when R^1 is a vinyl or ethynyl group, the R^1 substituent optionally bears at the terminal CH_2=, or HC≡ position a substituent selected from 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 :

$$Q^2-X^2-$$

wherein X^2 is a direct bond or is NHCO or N(Me)CO and Q^2 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 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 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-N-propylamino, acetoxy, acetamido and N-methylacetamido,

and wherein any phenyl, imidazolyl, triazolyl, pyridyl or heterocyclyl group within a substituent on R^1 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, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R^1 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, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

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

4. A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 wherein m is 1 and the R^1 group is located at the 5-position or m is 2 and the R^1 groups, which may be the same or different, are located at the 5- and 7-positions and each R^1 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, 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, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy, 3-homopiperazin-1-ylpropoxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy,

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

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more chloro groups or a substituent selected from hydroxy, oxo, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxy,

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

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

5. A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 wherein 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, 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, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, 2-piperidin-3-ylethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

and wherein any CH_2 or CH_3 group within a R^1 substituent optionally bears on each said CH_2 or CH_3 group one or more chloro groups or a substituent selected from hydroxy, oxo, amino, methoxy, methylsulphonyl, methylamino, dimethylamino, diisopropylamino, N-ethyl-N-methylamino, N-isopropyl-N-methylamino and acetoxy,

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

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

6. A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 wherein n is 1 and the R^3 group is located at the 5-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from fluoro, chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, methoxy and ethoxy.

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

Z is O or NH;

m is 1 and the R^1 group is located at the 5-, 6- or 7-position or m is 2 and the R^1 groups, which may be the same or different, are located at the 5- and 7-positions or at the 6- and 7-positions and each R^1 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 R^1 substituent are optionally separated by the insertion into the chain of a group selected from O, NH, N(Me), CH=CH and C≡C,

and when R^1 is a vinyl or ethynyl group, the R^1 substituent optionally bears at the terminal CH_2= or HC≡ position a substituent selected from 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 :

$$Q^2-X^2-$$

wherein X^2 is a direct bond or is NHCO or N(Me)CO and Q^2 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 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 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-N-propylamino, acetoxy, acetamido and N-methylacetamido,

and wherein any phenyl, imidazolyl, triazolyl, pyridyl or heterocyclyl group within a substituent on R^1 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, ethylidendioxy and isopropylidenedioxy, and a pyrrolidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl or homopiperazin-1-yl group within a R^1 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, 3-morpholinopropyl, 2-piperidinoethyl, 3-piperidinopropyl, 2-piperazin-1-ylethyl or 3-piperazin-1-ylpropyl, the last 8 of which substituents each optionally bears 1 or 2 substituents, which may be the same or different, selected from fluoro, chloro, methyl and methoxy,

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

n is 0 or n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from fluoro, chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, methoxy and ethoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

8. 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 a 6-methoxy group and the second R^1 group is located at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy, 3-[(3RS,4SR)-3,4-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, 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, 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, 3-methylsulphonylpropoxy, 2-(2-methoxyethoxy)ethoxy, 2-(4-pyridyloxy)ethoxy, 3-pyridylmethoxy and 2-cyanopyrid-4-ylmethoxy; and

n is 0 or n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from fluoro, chloro, bromo, trifluoromethyl and cyano;

or a pharmaceutically-acceptable acid-addition salt thereof.

9. 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, 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, 3-morpholinopropoxy, 4-morpholinobutoxy, 2-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)ethoxy, 3-(1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl)propoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 4-piperidinobutoxy, 2-piperidin-3-ylethoxy, 2-piperidin-4-ylethoxy, 2-homopiperidin-1-ylethoxy, 3-homopiperidin-1-ylpropoxy, 3-(1,2,3,6-tetrahydropyridin-1-yl)propoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-homopiperazin-1-ylethoxy and 3-homopiperazin-1-ylpropoxy,

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

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

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

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

n is 0 or n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from fluoro, chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, methoxy and ethoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

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

Z is NH;

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

or m is 2 and the first R^1 group is located at the 5-position and is selected from the group of substituents listed immediately above and the second R^1 group is located at the 7-position and is selected from 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-[(3RS,4SR)-3,4-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, 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, 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, 3-methylsulphonylpropoxy, 2-(2-methoxyethoxy)ethoxy, 2-(4-pyridyloxy)ethoxy, 3-pyridylmethoxy and 2-cyanopyrid-4-ylmethoxy;

n is 0 or n is 1 and the R^3 group is located at the 5- or 6-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from chloro, bromo, trifluoromethyl, cyano, hydroxy, methyl, ethyl, methoxy and ethoxy;

or a pharmaceutically-acceptable acid-addition salt thereof.

11. 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, 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-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 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-ynylpiperazın-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-hydroxyethyl)piperazin-1-yl]ethoxy, 3-[4-(2-hydroxyethyl)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-(2-dimethylaminoacetyl)piperazın-1-yl]ethoxy and 3-[4-(2-dimethylaminoacetyl)piperazin-1-yl]propoxy; and

n is 1 and the R^3 group is located at the 5-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from chloro and bromo;

or a pharmaceutically-acceptable acid-addition salt thereof.

12. 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, 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-allylpiperazın-1-yl)propoxy, 2-(4-prop-2-ynylpiperazin-1-yl)ethoxy, 3-(4-prop-2-ynylpiperazın-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

n is 1 and the R^3 group is located at the 5-position of the 2,3-methylenedioxypyridin-4-yl group and is selected from chloro and bromo;

or a pharmaceutically-acceptable acid-addition salt thereof.

13. 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, 2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperidinoethoxy, 2-piperazin-1-ylethoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 2-(4-prop-2-ynylpiperazin-1-yl)ethoxy, 3-(4-prop-2-ynylpiperazin-1-yl)propoxy, 2-(4-acetylpiperazin-1-yl)ethoxy, 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethoxy and 2-[4-(2-dimethylaminoacetyl)piperazin-1-yl]ethoxy; and

n is 1 and the R^3 group is located at the 5-position of the 2,3-methylenedioxypyridin-4-yl group and is a chloro group;

or a pharmaceutically-acceptable acid-addition salt thereof.

14. 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 a 5-isopropoxy group and the second R^1 group is located at the 7-position and is selected from 2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy, 2-piperazin-1-ylethoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 2-(4-acetylpiperazin-1-yl)ethoxy and 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethoxy; and

n is 1 and the R^3 group is located at the 5-position of the 2,3-methylenedioxypyridin-4-yl group and is a chloro group;

or a pharmaceutically-acceptable acid-addition salt thereof.

15. A quinazoline derivative of the Formula I according to claim 1 selected from :-

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxy-7-[3-(4-prop-2-ynylpiperazin-1-yl)propoxy]quinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-[3-(4-isobutyrylpiperazin-1-yl)propoxy]-6-methoxyquinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxy-7-{3-[4-(2,2,2-trifluoroethyl)piperazin-1-yl]propoxy}quinazoline and

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-6-methoxy-7-[2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]quinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

16. A quinazoline derivative of the Formula I according to claim 1 selected from :-

7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-tetrahydropyran-4-yloxyquinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[(3RS,4SR)-3,4-methylenedioxypyrrolidin-1-yl]ethoxy}-5-tetrahydropyran-4-yloxyquinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-[2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-[3-(4-prop-2-ynylpiperazin-1-yl)propoxy]-5-tetrahydropyran-4-yloxyquinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(2-morpholinoethoxy)-5-tetrahydropyran-4-yloxyquinazoline and

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-(3-morpholinopropoxy)-5-tetrahydropyran-4-yloxyquinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

17. A quinazoline derivative of the Formula I according to claim 1 selected from :-

7-[2-(4-acetylpiperazin-1-yl)ethoxy]-4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxyquinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxy-7-(2-piperazin-1-ylethoxy)quinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[4-(2-hydroxyethyl)piperazin-1-yl]ethoxy}-5-isopropoxyquinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxy-7-(2-pyrrolidin-1-ylethoxy)quinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxy-7-(2-piperidinoethoxy)quinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxy-7-(2-morpholinoethoxy)quinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxy-7-(3-morpholinopropoxy)quinazoline,

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxy-7-[2-(4-prop-2-ynylpiperazin-1-yl)ethoxy]quinazoline,

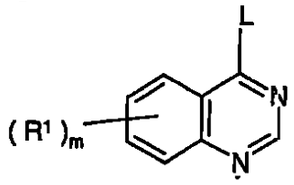
4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-5-isopropoxy-7-[2-(4-methylpiperazin-1-yl)ethoxy]quinazoline and

4-(5-chloro-2,3-methylenedioxypyrid-4-ylamino)-7-{2-[4-(2-dimethylaminoacetyl)piperazin-1-yl]ethoxy}-5-isopropoxyquinazoline;

or a pharmaceutically-acceptable acid-addition salt thereof.

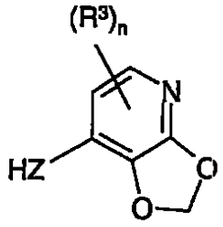
18. A process for the preparation of a quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 which comprises :-

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



II

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



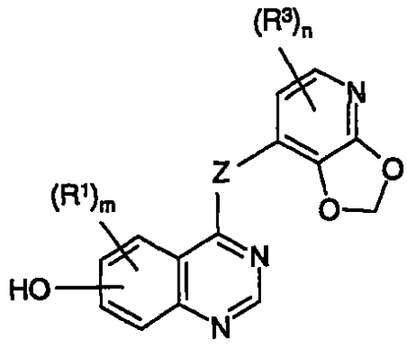
III

wherein Z is O, S, or N(R^2) and n, R^3 and R^2 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 group of the formula

$$Q^1\text{-}X^1\text{-}$$

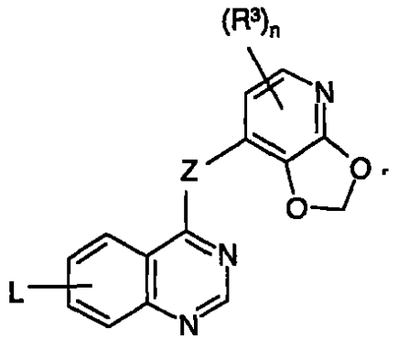
wherein Q^1 is an aryl-(1-6C)alkyl, (3-7C)cycloalkyl-(1-6C)alkyl, (3-7C)cycloalkenyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl or heterocyclyl-(1-6C)alkyl group or an optionally substituted alkyl group and X^1 is an oxygen atom, the coupling of a quinazoline of the Formula V



V

wherein m, R^1, Z, n and R^3 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;

(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



VI

wherein L is a displaceable group and Z, n and R^3 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;

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

(f) for the production of those compounds of the Formula I wherein Z is a SO or SO_2 group, the oxidation of a compound of Formula I wherein Z is a S group; or

(g) for the production of those compounds of the Formula I wherein an R^1 group contains an N-acylated heterocyclic group, the acylation of a quinazoline derivative of the Formula I wherein the R^1 group contains a heterocyclic group having an unsubstituted NH 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.

19. 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.

20. A quinazoline derivative of the Formula I, or a pharmaceutically-acceptable salt thereof, according to claim 1 for use in a method of treatment of the human or animal body by therapy.

21. 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.

22. A method for producing an anti-invasive effect by the containment and/or treatment of solid tumour disease in a warm-blooded animal 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, according to claim 1.

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/GB 03/04703

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D491/04 C07D519/00 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, PAJ, 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
Y	WO 95 15758 A (HSU CHIN YI JENNY; ZILBERSTEIN ASHER (US); JOHNSON SUSAN E (US); M) 15 June 1995 (1995-06-15) Abstract; page 3; claims.	1-22
Y	WO 97 03069 A (GLAXO GROUP LTD; COCKERILL GEORGE STUART (GB); CARTER MALCOLM CLIV) 30 January 1997 (1997-01-30) Abstract; page 6; claims.	1-22
Y	WO 02 16352 A (PLE PATRICK; HENNEQUIN LAURENT FRANCOIS AND (FR); LAMBERT CHRISTIN) 28 February 2002 (2002-02-28) cited in the application Abstract; pages 3-4; claims.	1-22

☐ 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	Date of mailing of the international search report
30 January 2004	10/02/2004

Name and mailing address of the ISA	Authorized officer
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	Weisbrod, T

Form PCT/ISA/210 (second sheet) (July 1992)

66

INTERNATIONAL SEARCH REPORT

ational application No
PCT/GB 03/04703

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

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

Although claim 22 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2 [ ] Claims Nos :
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically

3. [ ] Claims Nos :
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1 [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3 [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos .

4 [ ] No required additional search fees were timely paid by the applicant Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos :

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

- information on patent family members

Inte mal Application No
PCT/GB 03/04703

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9515758 A	15-06-1995	US	5480883 A	02-01-1996
		US	5710158 A	20-01-1998
		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	5795889 A	18-08-1998
		US	5646153 A	08-07-1997
		US	5721237 A	24-02-1998
		US	RE37650 E1	09-04-2002
		US	6645969 B1	11-11-2003
		US	5714493 A	03-02-1998
		US	6057320 A	02-05-2000
		US	RE36256 E	20-07-1999
WO 9703069 A	30-01-1997	AU	6613996 A	10-02-1997
		WO	9703069 A1	30-01-1997
		EP	0843671 A1	27-05-1998
		HR	960316 A1	28-02-1998
		JP	11508906 T	03-08-1999
		ZA	9605935 A	12-02-1998
WO 0216352 A	28-02-2002	AU	7860901 A	04-03-2002
		BR	0113358 A	01-07-2003
		CA	2419301 A1	28-02-2002
		CZ	20030486 A3	14-05-2003
		EP	1313727 A1	28-05-2003
		WO	0216352 A1	28-02-2002
		NO	20030795 A	04-04-2003
		SK	2142003 A3	01-07-2003

(12) SOLICITUD INTERNACIONAL PUBLICADA SEGÚN EL TRATADO DE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES (PCT)

67

(19) Organización Mundial de Propiedad Intelectual
Oficina Internacional

(43) Fecha de Publicación Internacional
21 de mayo de 2004 (21.05.2004)

(10) Número de Publicación Internacional

PCT WO 2004/041829 A1

(51) Clasificación Internacional de Patentes[7]: C07D 491/04. 519/00, A61K 31/517, A61P 35/00

(21) No. Solicitud Internacional: PCT/GB2003/004703

(22) Fecha de Presentación Internacional:
29 de octubre de 2003 (29 10 2003)

(25) Idioma de Presentación. Inglés

(26) Idioma de Publicación: Inglés

(30) Datos relativos a la Prioridad:
02292736 2 4 de noviembre de 2002 (04 11 2002) EP
03290900 4 10 de abril de 2003 (10 04 2003) EP

(71) Solicitante *(para AE, AG, AL, AM, AT, AU, AZ, BA, BB, BE, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CY, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, FR, GB, GD, GE, GH, GM, GR, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, SZ, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW únicamente)* **ASTRAZENECA AB** [SE/SE], Sodertalje, S-151 85 (SE)

(71) Solicitante *(para MG únicamente)* **ASTRAZENECA UK LIMITED** [GB/GB], 15 Stanhope Gate, London, Greater London W1K 1LN (GB)

(72) Inventores, e

(75) Inventores/Solicitantes *(para US únicamente)*: **PLE, Patrick** [FR/FR], AstraZeneca Pharma, Z I La Pompelle, BP 1050, F-51689 Reims Cedex 2 (FR)

(74) Agente. **TAIT, Brian, Steele**, ASTRAZENECA, Global Intellectual Property, P O Box 272, Mereside, Macclesfield, Cheshire SK10 4GR (GB)

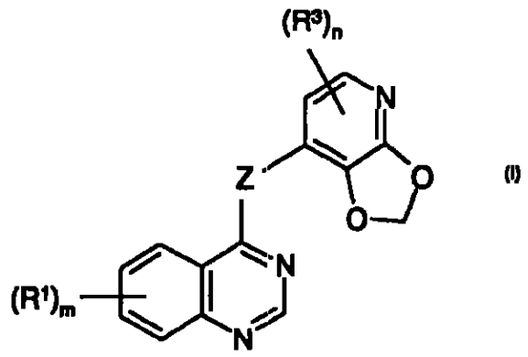
(81) Países designados *(nacionales)* AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, 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) Países designados *(regionales)* Patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Patente Eurasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Publicado:
— *con informe internacional de búsqueda*

Para códigos de dos letras y otras abreviaturas, remítase a las "Notas Guía sobre Códigos y Abreviaturas" que aparece al comienzo de cada edición regular del Boletín Oficial PCT

(54) Título: DERIVADOS DE QUINAZOLINA COMO INHIBIDORES DE SRC TIROSINA CINASA



(57) Extracto: La invención concierne a derivados de quinazolina de Fórmula (I) (Debe insertarse aquí una fórmula química – ver, por favor, la copia del documento incluida con el presente) en donde Z es un grupo O, S, SO, SO_2, $N(R^2)$ ó $C(R^2)_2$ en donde cada grupo R^2 es hidrógeno o (1-8C) alquilo, m es 0, 1, 2 ó 3, cada grupo R^1 se selecciona de halógeno, (1-8C) alquilo, (1-6C) alcoxi y cualquiera de los otros significados definidos en la descripción, n es 0, 1, 2 ó 3, y cada grupo R^3 se selecciona de halógeno, (1-8C) alquilo, (1-6C) alcoxy y cualquiera de los otros significados definidos en la descripción, o sus sales farmacéuticamente aceptables, procesos para su preparación, composiciones farmacéuticas que los contienen y su uso en la manufactura de un medicamento para uso como agente anti-invasivo en la contención y/o tratamiento de enfermedad de tumor sólido

WO 2004/041829 A1

68

DERIVADOS DE QUINAZOLINA COMO INHIBIDORES DE SRC TIROSINA CINASA

La invención concierne a ciertos derivados novedosos de quinazolina, o a sus sales farmacéuticamente aceptables, que poseen actividad anti-neoplásica y, por consiguiente, son útiles en métodos de tratamiento del cuerpo humano o animal. La invención se relaciona asimismo con procesos para la manufactura de dichos derivados de quinazolina, a composiciones farmacéuticas que los contienen y a su uso en métodos terapéuticos, por ejemplo en la manufactura de medicamentos para uso en la prevención o tratamiento de enfermedad de tumor sólido en un animal de sangre caliente como el hombre.

Muchos de los regímenes actuales de tratamiento para las enfermedades de proliferación celular, tal como psoriasis y cáncer, utilizan compuestos que inhiben la síntesis del ADN. Tales compuestos son generalmente citotóxicos pero su efecto tóxico puede ser benéfico en células que se dividen rápidamente tales como las células cancerosas. Enfoques alternativos a agentes antineoplásicos que actúan mediante mecanismos diferentes a la inhibición de la síntesis del ADN poseen el potencial de desplegar una selectividad de acción mejorada.

En años recientes se ha descubierto que una célula puede volverse cancerosa en virtud de la transformación de una porción de su ADN en un oncogén *es decir,* un gen que, al activarse, lleva a la formación de células tumorales malignas (Bradshaw, Mutagenesis, 1986, 1, 91). Varios de tales oncogenes dan lugar a la producción de péptidos que son receptores de factores de crecimiento. La activación del complejo de receptores de factores de crecimiento lleva posteriormente a un aumento en la proliferación celular. Se sabe, por ejemplo, que varios oncogenes codifican enzimas tirosina cinasas y que ciertos receptores de factor de crecimiento son también enzimas tirosina cinasas (Yarden *et al*, Ann. Rev. Biochem.. 1988, 57, 443; Larsen *et al.*, Ann. Reports in Med. Chem., 1989, Chpt. 13). El primer grupo de tirosina cinasas en ser identificado surgió de tales

oncogenes virales, por ejemplo $pp60^{v\text{-}Src}$ tirosina cinasa (conocida en otra forma como v-Src), y las correspondientes tirosina cinasas en células normales, por ejemplo $pp60^{c\text{-}Src}$ tirosina cinasa (conocida en otra forma como c-Src).

Las tirosina cinasas de receptor son importantes en la transmisión de señales bioquímicas que inician la replicación celular. Son grandes enzimas que se extienden por toda la membrana celular y poseen un dominio de fijación extracelular para factores de crecimiento tales como el factor de crecimiento epidérmico (EGF) y una porción intracelular que funciona como una cinasa para fosforilar aminoácidos de tirosina en proteínas y, por lo tanto, influir en la proliferación celular. Se conocen varias clases de tirosina cinasas de receptor (Wilks, Advances in Cancer Research. 1993, 60, 43-73) basadas en familias de factores de crecimiento que se unen a diferentes tirosina cinasas de receptor. La clasificación incluye tirosina cinasas de receptor Clase I que comprenden la familia EGF de tirosina cinasas de receptor tales como los receptores EGF, TGFα, Neu y erbB, las tirosina cinasas de receptor Clase II que comprenden la familia insulina de tirosina cinasas de receptor tales como los receptores de insulina y IGF1 y el receptor relacionado con la insulina (IRR) y las tirosina cinasas de recetor Clase III que comprenden la familia del factor de crecimiento derivado de plaquetas (PDGF) de tirosina cinasas de receptor tales como los receptores PDGFα, PDGFβ y factor 1 estimulador de colonias (CSF1).

Se sabe también que ciertas tirosina cinasas pertenecen a la clase de tirosina cinasas de no receptor, las cuales se localizan intracelularmente y están involucradas en la transmisión de señales bioquímicas tales como las que influyen en la motilidad de las células cancerosas, la diseminación e invasividad y, posteriormente, crecimiento neoplásico metastásico (Ullrich *et al,* Cell, 1990, 61, 203-212, Bolen *et al,* FASEB J., 1992, 6, 3403-3409, Brickell *et al.*, Critical Reviews in Oncogenesis. 1992, 3, 401-406, Bohlen *et al.*, Oncogene. 1993, 8, 2025-2031, Courtneidge *et al.*, Semin. Cancer Biol., 1994, 5, 239-246, Lauffenburger *et al.*, Cell, 1996, 84, 359-369, Hanks *et al.*, BioEssays, 1996, 19, 137-145, Parsons *et al.*, Current Opinion

in Cell Biology, 1997, 9, 187-192, Brown *et al.*, Biochimica et Biophysica Acta. 1996, 1287, 121-149 y Schlaepfer *et al.*, Progress in Biophysics and Molecular Biology, 1999, 71, 435-478). Se conocen varias clases de tirosina cinasas de no receptor, incluida la familia Src, tal como las tirosina cinasas Src, Lyn y Yes, la familia Abl tal como Abl y Arg y la familia Jak tal como Jak 1 y Tyk 2.

Se sabe que la familia Src de tirosina cinasas de no receptor está altamente regulada en las células normales y, en ausencia de estímulos extracelulares, se mantiene en una conformación inactiva. Sin embargo, algunos miembros de la familia Src, por ejemplo la tirosina cinasa c-Src, están frecuentemente activados de manera significativa (cuando se comparan con los niveles de células normales) en cánceres humanos comunes, tal como el cáncer gastrointestinal, por ejemplo, cáncer de colon, del recto y del estómago (Cartwright *et al.*, Proc. Natl. Acad. Sci USA, 1990, 87, 558-562 y Mao *et al.*, Oncogene, 1997, 15, 3083-3090), y cáncer de mama (Muthuswamy *et al.*, Oncogene. 1995, 11, 1801 -1810). La familia Src de tirosina cinasas de no receptor se ha localizado igualmente en otros cánceres humanos comunes tales como carcinomas pulmonares amicrocíticos (NSCLCs) incluidos adenocarcinomas y carcinoma escamoso del pulmón (Mazurenko *et al.*, European Journal of Cancer, 1992, 28, 372-7), cáncer de la vejiga (Fanning *et al.*, Cancer Research. 1992, 52, 1457-62), cáncer del esófago (Jankowski *et al.*, Gut, 1992, 33, 1033-8), cáncer de la próstata, cáncer de los ovarios (Wiener *et al.*, Clin. Cancer Research, 1999, 5, 2164-70) y cáncer del páncreas (Lutz *et al.*, Biochem. And Biophys. Res. Comm., 1998, 243, 503-8). A medida que se examinen otros tejidos humanos para detectar la presencia de la familia Src de tirosina cinasas de no receptor, se espera que se establezca su difundida prevalencia.

Se sabe también que el papel predominante de la tirosina cinasa de no receptor c-Src consiste en regular el ensamble de complejos de adhesión focal a través de la interacción con un número de proteínas citoplásmicas incluidas, por ejemplo, cinasa de adhesión focal y paxilina. Además, la c-Src se acopla a las vías de señalización que regulan el citoesqueleto de la

actina lo cual facilita la motilidad celular. Análogamente, se ejercen papeles importantes por las tirosina cinasas de no receptor c-Src, c-Yes y c-Fyn en la señalización mediada por la integrina y en romper las uniones célula a célula dependientes de la cadherina (Owens *et al.*, Molecular Biology of the Cell, 2000, 11, 51-64 y Klinghoffer *et al.*, EMBO Journal. 1999, 18, 2459-2471). La motilidad celular se requiere necesariamente para que un tumor localizado pase por las etapas de diseminación en el torrente sanguíneo, invasión de otros tejidos e iniciación del crecimiento neoplásico metastásico. Por ejemplo, la evolución de un tumor del colon de localizado a diseminado, la enfermedad metastásica invasiva se ha correlacionado con actividad de tirosina cinasa de no receptor c-Src (Brunton *et al.*, Oncogene. 1997, 14, 283-293, Fincham *et al.*, EMBO J, 1998, 17, 81-92 y Verbeek *et al.*, Exp. Cell Research. 1999, 248, 531-537).

Por consiguiente, se ha reconocido que un inhibidor de tales tirosina cinasas de no receptor debe ser útil como inhibidor selectivo de la motilidad de las células cancerosas y como inhibidor selectivo de la diseminación e invasividad de células cancerígenas de mamífero que lleva a la inhibición de crecimiento neoplásico metastásico. En particular, un inhibidor de tales tirosina cinasas de no receptor debe ser valioso como agente anti-invasivo para uso en la contención y/o tratamiento de enfermedad de tumor sólido.

Ahora hemos descubierto que, sorprendentemente, ciertos derivados de quinazolina poseen potente actividad anti-neoplásica. Sin querer implicar que los compuestos divulgados en la presente invención poseen actividad farmacológica únicamente en virtud de un efecto sobre un proceso biológico único, se cree que los compuestos producen un efecto anti-neoplásico mediante la inhibición de una o más de las proteína cinasas específicas de tirosina de no receptor que están involucradas en los pasos de transducción de señales, que llevan a la invasividad y capacidad migratoria de células cancerosas metastásicas. En particular, se cree que los compuestos de la presente invención proporcionan un efecto anti-neoplásico mediante la inhibición de la familia Src de tirosina cinasas de no receptor, por ejemplo mediante la inhibición de una o más de c-Src, c-Yes y c-Fyn.

Se sabe igualmente que la enzima tirosina cinasa de no receptor c-Src se halla involucrada en el control de la resorción ósea inducida por osteoclastos (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 y Missbach *et al.*, Bone, 1999, 24, 437-49). Por lo tanto, un inhibidor de la tirosina cinasa de no receptor c-Src es útil en la prevención y tratamiento de enfermedades óseas tales como osteoporosis, osteítis deformante (***"Paget's disease"***), enfermedad metastásica en los huesos e hipercalcemia inducida por tumores.

Los compuestos de la presente invención so igualmente útiles en inhibir la proliferación celular incontrolada que surge de varias enfermedades no malignas tales como enfermedades inflamatorias (por ejemplo, artritis reumatoide y enfermedad inflamatoria intestinal), enfermedades fibróticas (por ejemplo cirrosis hepática y fibrosis pulmonar), glomerulonefritis, esclerosis múltiple, psoriasis, reacciones de hipersensibilidad de la piel, enfermedades de los vasos sanguíneos (por ejemplo ateroesclerosis y restenosis), asma alérgico, diabetes insulinodependiente, retinopatía diabética y nefropatía diabética;

Por lo general, los compuestos de la presente invención poseen una potente actividad inhibidora contra la familia Src de tirosina cinasas de no receptor, por ejemplo mediante la inhibición de c-Src y/o c-Yes, mientras que poseen actividad inhibidora menos potente contra otras enzimas tirosina cinasas tales como las tirosina cinasas de receptor, por ejemplo tirosina cinasas de receptor EGF y/o tirosina cinasa de receptor VEGF.

Más aún, ciertos compuestos de la presente invención poseen sustancialmente una mejor potencia contra la familia Src de tirosina cinasas de no receptor, por ejemplo c-Src y/o c-Yes, que contra tirosina cinasas de receptor VEGF. Tales compuestos poseen suficiente potencia contra la familia Src de tirosina cinasas de no receptor, por ejemplo, c-Src y/o c-Yes, de manera que pueden usarse en una cantidad suficiente para inhibir, por ejemplo, c-Src y/o c-Yes demostrando al mismo tiempo poca actividad contra tirosina cinasa de receptor VEGF. Es beneficioso reducir al mínimo

73

la actividad inhibidora de la tirosina cinasa de receptor VEGF, puesto que se ha descubierto que algunos compuestos con esa actividad, actúan como bloqueadores de los canales de potasio, por ejemplo, en un análisis de canal de potasio codificado por el gen humano relacionado ether-a-go-go (hERG). Tal actividad puede dar lugar a cambios en el electrocardiograma (ECG) *in vivo*.

El tratamiento anti-neoplásico definido más adelante puede aplicarse como terapia individual o puede involucrar, aparte del derivado de quinazolina de la invención, cirugía o radioterapia o quimioterapia convencionales. Es bien sabido que casi todos los fármacos se metabolizan en cierto grado en el humano, generalmente en un compuesto menos soluble en lípidos, el cual se excreta más fácilmente por el riñón. Muchas de las enzimas metabólicas de los fármacos se encuentran en el retículo endoplásmico (que formas microsomas con la homogeneización) de los hepatocitos. El hígado es el principal sitio de metabolismo de los fármacos porque las células hepáticas (hepatocitos) contienen concentraciones particularmente elevadas de enzimas metabolizantes de los fármacos. Citocromo P450 es una familia de isoenzimas hallada en los microsomas hepáticos. Seis isoenzimas P450 específicas son responsables del metabolismo de la mayoría de los fármacos usados más comúnmente, a saber P450 1A2, 2C9, 2C19, 2D6, 2E1 y 3A4. La quimioterapia de combinación puede ser problemática si uno o más de los fármacos componentes de la combinación se metabolizan por el Citocromo P450 3A4 (en lo sucesivo CYP 3A4). Tal componente puede ser un sustrato de CYP 3A4 o puede ser un inductor o un inhibidor de esa isoenzima. Tales efectos pueden afectar la farmacocinética del otro componente de la terapia de combinación.

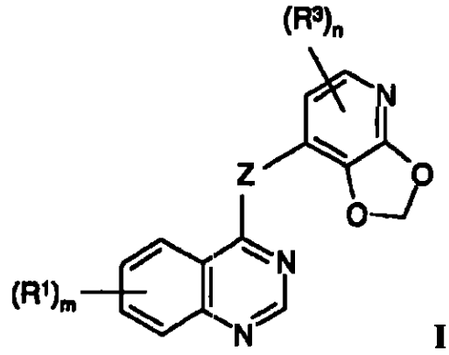
Hemos establecido que ciertos compuestos de la presente invención poseen la ventajosa propiedad de ser menos susceptibles al metabolismo por tales isoenzimas P450, particularmente por CYP 3A4. En consecuencia, es posible administrar tales compuestos en terapia anti-neoplásica de combinación con mayor seguridad.

Además, hemos establecido que ciertos compuestos de la presente invención son doblemente ventajosos porque poseen poca actividad contra la tirosina cinasas de receptor VEGF y muestran poca o ninguna tendencia a ser metabolizados por las isoenzimas P450 tales como CYP 3A4.

Se indica en la Solicitud Internacional de Patente WO 01/94341 que un rango de derivados de quinazolina son útiles en el tratamiento del cáncer. Se declara que los compuestos poseen actividad inhibidora contra la familia Src de tirosina cinasas de no receptor. Se divulgan allí ciertos derivados de quinazolina 5-sustituidos incluidos ciertas 4-(2,3-metilendioxianilino)quinazolinas 5-sustituidas. No se divulgan allí derivados de 4-(2,3-metilendioxipirid-4-ilamino)quinazolina de ningún tipo.

Se especifica en la Solicitud Internacional de Patente WO 02/16352 que un rango de derivados de 4-(2,3-metilendioxianilino)quinazolina son útiles en el tratamiento del cáncer. Se establece que los compuestos poseen actividad inhibidora contra la familia Src de tirosina cinasas de no receptor. No se divulgan allí derivados de 4-(2,3-metilendioxipirid-4-ilamino) quinazolina de ningún tipo.

De acuerdo con un aspecto de la invención se provee un derivado de quinazolina de la Fórmula I



I

en donde **Z** es un grupo O, S, SO, SO_2, $N(R^2)$ o $C(R^2)_2$ en donde cada grupo R^2, los cuales pueden ser los mismos o diferentes, es hidrógeno o (1-8C)alquilo;

m es 0, 1, 2 ó 3;

cada grupo R^1, los cuales pueden ser los mismos o diferentes, se

selecciona de halógeno trifluorometilo, ciano, isociano, nitro, hidroxi, mercapto, amino, formilo, carboxi, carbamoilo, (1-8C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, (3-6C)alquenoilamino, N-(1-6C)alquil-(3-6C)alquenoilamino, (3-6C)alquinoilamino, N-(1-6C)alquil-(3-6C)alquinoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:

$$Q^1 - X^1 -$$

en donde X^1 es un enlace directo o se selecciona de O, S, SO, SO_2, $N(R^4)$, CO, $CH(OR^4)$, $CON(R^4)$, $N(R^4)CO$, $SO_2N(R^4)$, $N(R^4)SO_2$, $OC(R^4)_2$, $SC(R^4)_2$ y $N(R^4)C(R^4)_2$, en donde R^4 es hidrógeno o (1-8C)alquilo, y Q^1 es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo, o $(R^1)_m$ es (1-3C)alquilenodioxi,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileno dentro de un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, S, SO, SO_2, $N(R^5)$, CO, $CH(OR^5)$, $CON(R^5)$, $N(R^5)CO$, $SO_2N(R^5)$, $N(R^5)SO_2$, CH=CH y C≡C en donde R^5 es hidrógeno o (1-8C)alquilo o, cuando el grupo insertado es $N(R^5)$, R^5 puede ser también (2-6C)alcanoilo,

y en donde cualquier grupo CH_2=CH- o HC≡C- dentro de un sustituyente R^1 lleva opcionalmente en la posición terminal CH_2= o HC≡ un sustituyente seleccionado de halógeno carboxi, carbamoilo, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo y di-[(1-6C)alquil]amino-(1-6C)alquilo o de un grupo de la

fórmula:

$$Q^2 - X^2 -$$

en donde X^2 es un enlace directo o se selecciona de CO y $N(R^6)CO$, en donde R^6 es hidrógeno o (1-8C)alquilo, y Q^2 es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde cualquier CH_2 o CH_3 dentro de un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 o CH_3 uno o más sustituyentes halógeno o (1-8C)alquilo o un sustituyente seleccionado de hidroxi, ciano, amino, carboxi, carbamoilo, oxo, tioxo, (1-6C)alcoxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:

$$-X^3-Q^3$$

en donde X^3 es un enlace directo o se selecciona de O, S, SO, SO_2, $N(R^7)$, CO, $CH(OR^7)$, $CON(R^7)$, $N(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, $C(R^7)_2O$, $C(R^7)_2S$ y $N(R^7)C(R^7)_2$, en donde R^7 es hidrógeno o (1-8C)alquilo, y Q^3 es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde cualquier grupo arilo, heteroarilo o heterociclilo dentro de un sustituyente R^1 lleva opcionalmente 1, 2 ó 3 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de halógeno, trifluorometilo, ciano, nitro, hidroxi, amino, carboxi, carbamoilo, (1-8C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-

6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino, N-(1-6C)alquil-(1-6C)alcanosulfonilamino y (1-3C)alquilenodioxi, o de un grupo de la fórmula:

$$-X^4-R^8$$

en donde X^4 es un enlace directo o se selecciona de O y $N(R^9)$, en donde R^9 es hidrógeno o (1-8C)alquilo, y R^8 es halógeno-(1-6C)alquilo, hidroxi-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, (2-6C)alcanoilamino-(1-6C)alquilo o (1-6C)alcoxicarbonilamino-(1-6C)alquilo, o de un grupo de la fórmula:

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

en donde X^5 es un enlace directo o se selecciona de O, $N(R^{10})$ y CO, en donde R^{10} es hidrógeno o (1-8C)alquilo, y Q^4 es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de halógeno (1-8C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo y (1-6C)alcoxi,

y en donde cualquier grupo heterociclilo dentro de un sustituyente R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo;

n es 0, 1, 2 ó 3; y

cada grupo R^3, los cuales pueden ser los mismos o diferentes, se selecciona de halógeno trifluorometilo, ciano, nitro, hidroxi, amino, carboxi, carbamoilo, (1-8C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, (3-6C)alquenoilamino, N-(1-6C)alquil-(3-6C)alquenoilamino, (3-

6C)alquinoilamino, N-(1-6C)alquil-(3-6C)alquinoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:

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

en donde X^6 es un enlace directo o se selecciona de O y $N(R^{12})$, en donde R^{12} es hidrógeno o (1-8C)alquilo, y R^{11} es halogeno-(1-6C)alquilo, hidroxi-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo o di-[(1-6C)alquil]amino-(1-6C)alquilo, o de un grupo de la fórmula:

$$-X^7 - Q^5$$

en donde X^7 es un enlace directo o se selecciona de O, S, SO, SO_2, $N(R^{13})$, CO, $CH(OR^{13})$, $CON(R^{13})$, $N(R^{13})CO$, $SO_2N(R^{13})$, $N(R^{13})SO_2$, $C(R^{13})_2O$, $C(R^{13})_2S$ y $N(R^{13})C(R^{13})_2$, en donde R^{13} es hidrógeno o (1-8C)alquilo, y Q^5 es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de halógeno (1-8C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo y (1-6C)alcoxi, y cualquier grupo heterociclilo dentro de Q^5 lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo;

o su sal farmacéuticamente aceptable.

De acuerdo con un aspecto adicional de la invención se provee un derivado de quinazolina de la Fórmula I como se define anteriormente en donde Z es O, S, SO, SO_2, CH_2 ó NH;

m es 0, 1, 2 ó 3;

cada grupo R^1, los cuales pueden ser los mismos o diferentes, se selecciona de halógeno trifluorometilo, ciano, isociano, nitro, hidroxi, mercapto, amino, formilo, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-

6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, (3-6C)alquenoilamino, N-(1-6C)alquil-(3-6C)alquenoilamino), (3-6C)alquinoilamino, N-(1-6C)alquil-(3-6C)alquinoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:

$$Q^1\text{-}X^1\text{-}$$

en donde X^1 es un enlace directo o se selecciona de O, S, SO, SO_2, $N(R^4)$, CO, $CH(OR^4)$, $CON(R^4)$, $N(R^4)CO$, $SO_2N(R^4)$, $N(R^4)SO_2$, $OC(R^4)_2$, $SC(R^4)_2$ y $N(R^4)C(R^4)_2$, en donde R^4 es hidrógeno o (1-6C)alquilo, y Q^1 es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo, o $(R^1)_m$ es (1-3C)alquilenodioxi,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileno dentro de un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, S, SO, SO_2, $N(R^5)$, CO, $CH(OR^5)$, $CON(R^5)$, $N(R^5)CO$, $SO_2N(R^5)$, $N(R^5)SO_2$, CH=CH y C≡C en donde R^5 es hidrógeno o (1-6C)alquil o, cuando el grupo insertado es $N(R^5)$, R^5 puede ser también (2-6C)alcanoilo,

y en donde cualquier grupo CH_2=CH- o HC≡C- dentro de un sustituyente R^1 lleva opcionalmente en la posición terminal CH_2= o HC≡ un sustituyente seleccionado de halógeno carboxi, carbamoilo, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo y di-[(1-6C)alquil]amino-(1-6C)alquilo o de un grupo de la fórmula:

$$Q^2\text{-}X^2\text{-}$$

en donde X^2 es un enlace directo o se selecciona de CO y $N(R^6)CO$, en donde R^6 es hidrógeno o (1-6C)alquilo, y Q^2 es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde cualquier grupo CH_2 ó CH_3 dentro de un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 uno o más sustituyentes halógeno o (1-6C)alquilo o un sustituyente seleccionado de hidroxi, ciano, amino, carboxi, carbamoilo, oxo, tioxo, (1-6C)alcoxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C) alcanosulfonilamino, o de un grupo de la fórmula:

$$-X^3 - Q^3$$

en donde X^3 es un enlace directo o se selecciona de O, S, SO, SO_2, $N(R^7)$, CO, $CH(OR^7)$, $CON(R^7)$, $N(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, $C(R^7)_2O$, $C(R^7)_2S$ y $N(R^7)C(R^7)_2$, en donde R^7 es hidrógeno o (1-6C)alquilo, y Q^3 es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde cualquier grupo arilo, heteroarilo o heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1, 2 ó 3 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionado de halógeno trifluorometilo, ciano, nitro, hidroxi, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino, N-(1-6C)alquil-(1-6C)alcanosulfonilamino y (1-3C)alquilenodioxi, o de un grupo de la fórmula:

81

$-X^4-R^8$

en donde X^4 es un enlace directo o se selecciona de O y $N(R^9)$, en donde R^9 es hidrógeno o (1-6C)alquilo, y R^8 es halógeno-(1-6C)alquilo, hidroxi-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, (2-6C)alcanoilamino-(1-6C)alquilo o (1-6C)alcoxicarbonilamino-(1-6C)alquilo, o de un grupo de la fórmula:

$-X^5-Q^4$

en donde X^5 es un enlace directo o se selecciona de O, $N(R^{10})$ y CO, en donde R^{10} es hidrógeno o (1-6C)alquilo, y Q^4 es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de halógeno (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo y (1-6C)alcoxi,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo;

n es 0, 1, 2 ó 3; y

cada grupo R^3, los cuales pueden ser los mismos o diferentes, se selecciona de halógeno trifluorometilo, ciano, nitro, hidroxi, amino, carboxi, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, (3-6C)alquenoilamino, N-(1-6C)alquil-(3-6C)alquenoilamino, (3-6C)alquinoilamino, N-(1-6C)alquil-(3-6C)alquinoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:

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

en donde X^6 es un enlace directo o se selecciona de O y $N(R^{12})$, en donde

R^{12} es hidrógeno o (1-6C)alquilo, y R^{11} es halógeno-(1-6C)alquilo, hidroxi-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo o di-[(1-6C)alquil]amino-(1-6C)alquilo, o de un grupo de la fórmula:

$$-X^7 - Q^5$$

en donde X^7 es un enlace directo o se selecciona de O, S, SO, SO_2, $N(R^{13})$, CO, $CH(OR^{13})$, $CON(R^{13})$, $N(R^{13})CO$, $SO_2NCR^{13})$, $N(R^{13})SO_2$, $C(R^{13})_2O$, $C(R^{13})_2S$ y $N(R^{13})C(R^{13})_2$, en donde R^{13} es hidrógeno o (1-6C)alquilo, y Q^5 es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de halógeno (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo y (1-6C)alcoxi, y cualquier grupo heterociclilo dentro de Q^5 lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo;

o su sal farmacéuticamente aceptable.

En esta especificación el término genérico "alquilo" incluye los dos grupos alquilo de cadena recta y cadena ramificada tales como propilo, isopropilo y tert-butilo, y además grupos (3-7C)cicloalquilo tales como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y cicloheptilo, y también grupos (3-7C)cicloalquil-(1-2C)alquilo tales como ciclopropilmetilo, 2-ciclopropiletilo, ciclobutilmetilo, 2-ciclobutiletilo, ciclopentilmetilo, 2-ciclopentiletilo, ciclohexilmetilo y 2-ciclohexiletilo. No obstante, las referencias a grupos alquilo individuales tales como "propilo" son específicos para la versión de cadena recta únicamente; las referencias a grupos alquilo individuales de cadena ramificada tales como "isopropilo" son específicos para la versión de cadena ramificada únicamente y las referencias a grupos cicloalquilo individuales tales como "ciclopentilo" son específicos para ese anillo de 5 miembros únicamente. Una convención análoga se aplica a otros términos genéricos, por ejemplo (1-6C)alcoxi incluye grupos (3-6C)cicloalquiloxi y grupo s(3-5C)cicloalquil-(1-2C)alcoxi, por ejemplo metoxi, etoxi, propoxi, isopropoxi, ciclopropiloxi, ciclobutiloxi, ciclopentiloxi, ciclohexiloxi, ciclopropilmetoxi, 2-

ciclopropiletoxi, ciclobutilmetoxi, 2-ciclobutiletoxi y ciclopentilmetoxi; (1-6C)alquilamino incluye grupos (3-6C)cicloalquilamino y grupos (3-5C)cicloalquil-(1-2C)alquilamino, por ejemplo metilamino, etilamino, propilamino, ciclopropilamino, ciclobutilamino, ciclohexilamino, ciclopropilmetilamino, 2-ciclopropiletilamino, ciclobutilmetilamino, 2-ciclobutiletilamino y ciclopentilmetilamino; y di-[(1-6Calquil]amino incluye grupos di-[(3-6C)cicloalquil]amino y grupos di-[(3-5C)cicloalquil-(1-2C)alquil]amino, por ejemplo dimetilamino, dietilamino, dipropilamino, N-ciclopropil-N-metilamino, N-ciclobutil-N-metilamino, N-ciclohexil-N-etilamino, N-ciclopropilmetil-N-metilamino, N-(2-ciclopropiletil)-N-metilamino y N-ciclopentilmetil-N-metilamino.

Hay que entender que, en la medida en que algunos de los compuestos de Fórmula I definidos arriba pueden existir en formas ópticamente activas o racémicas en virtud de uno o más átomos de carbono asimétricos, la invención incluye en su definición cualquier forma ópticamente activa o racémica similar, que posea la actividad mencionada anteriormente. La síntesis de formas ópticamente activas puede llevarse a cabo por técnicas estándar de química orgánica bien conocidas en el arte, por ejemplo mediante síntesis de materiales de partida ópticamente activos o mediante resolución de una forma racémica. Análogamente, la actividad ya mencionada puede evaluarse usando las técnicas estándar de laboratorio mencionadas más adelante.

Valores apropiados de los radicales genéricos indicados más arriba incluyen los expuestos a continuación.

Un valor apropiado para uno cualquiera de los grupos 'Q' (Q^1 a Q^5) cuando es arilo o para el grupo arilo dentro de un grupo 'Q' es, por ejemplo, fenilo o naftilo, preferiblemente fenilo.

Un valor apropiado para uno cualquiera de los grupos 'Q' (Q^1 ó Q^3) cuando es (3-7C)cicloalquilo o para el grupo (3-7C)cicloalquilo dentro de un grupo 'Q' es, por ejemplo, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo o biciclo[2.2.1]heptilo y un valor apropiado para uno cualquiera de los grupos 'Q' (Q^1 ó Q^3) cuando es (3-7C)cicloalquenilo o

para el grupo (3-7C)cicloalquenilo dentro de un grupo 'Q' es, por ejemplo, ciclobutenilo, ciclopentenilo, ciclohexenilo o cicloheptenilo.

Un valor apropiado para uno cualquiera de los grupos 'Q' (Q^1 a Q^5) cuando es heteroarilo o para el grupo heteroarilo dentro de un grupo 'Q' es, por ejemplo, un anillo monocíclico de 5 ó 6 miembros, aromático, o un anillo bicíclico de 9 ó 10 miembros con hasta cinco heteroátomos del anillo, seleccionados de oxígeno, nitrogeno y azufre, por ejemplo furilo, pirrolilo, tienilo, oxazolilo, isoxazolilo, imidazolilo, pirazolilo, tiazolilo, isotiazolilo, oxadiazolilo, tiadiazolilo, triazolilo, tetrazolilo, piridilo, piridazinilo, pirimidinilo, pirazinilo, 1,3,5-triazenilo, benzofuranilo, indolilo, benzotienilo, benzoxazolilo, benzimidazolilo, benzotiazolilo, indazolilo, benzofurazanilo, quinolilo, isoquinolilo, quinazolinilo, quinoxalinilo, cinnolinilo o naftiridinilo.

Un valor apropiado para uno cualquiera de los grupos 'Q' (Q^1 a Q^5) cuando es heterociclilo o para el grupo heterociclilo dentro de un grupo 'Q' es, por ejemplo, un anillo monocíclico o bicíclico de 3 a 10 miembros saturado o parcialmente saturado, no aromático, con hasta cinco heteroátomos seleccionados de oxígeno, nitrógeno y azufre, por ejemplo oxiranilo, oxetanilo, tetrahidrofuranilo, tetrahidropiranilo, oxepanilo, tetrahidrotienilo, 1,1-dioxotetrahidrotienilo, tetrahidrotiopiranilo, 1,1-dioxotetrahidrotiopiranilo, azetidinilo, pirrolinilo, pirrolidinilo, morfolinilo, tetrahidro-1,4-tiazinilo, 1,1-dioxotetrahidro-1,4-tiazinilo, piperidinilo, homopiperidinilo, piperazinilo, homopiperazinilo, dihidropiridinilo, tetrahidropiridinilo, dihidropirimidinilo o tetrahidropirimidinilo, preferiblemente tetrahidrofuranilo, tetrahidropiranilo, pirrolidinilo, morfolinilo, 1,1-dioxotetrahidro-4H-1,4-tiazinilo, piperidinilo o piperazinilo. Un valor apropiado para tal grupo que lleva 1 ó 2 sustituyentes oxo o tioxo es, por ejemplo, 2-oxopirrolidinilo, 2-tioxopirrolidinilo, 2-oxoimidazolidinilo, 2-tioxoimidazolidinilo, 2-oxopiperidinilo, 2,5-dioxopirrolidinilo, 2,5-dioxoimidazolidinilo o 2,6-dioxopiperidinilo.

Un valor apropiado para un grupo 'Q' cuando es heteroaril-(1-

6C)alquilo es, por ejemplo, heteroarilmetilo, 2-heteroariletilo y 3-heteroarilpropilo. La invención comprende valores correspondientes apropiados para los grupos 'Q' cuando, por ejemplo, en lugar de un grupo heteroaril-(1-6C)alquilo, está presente un grupo aril-(1-6C)alquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenil-(1-6C)alquilo o heterociclil-(1-6C)alquilo.

Hay que entender que hay un átomo de hidrógeno en la posición 2 en el anillo de quinazolina en la Fórmula estructural I. Por esa razón, los sustituyentes R^1 sólo pueden localizarse en las posiciones 5, 6, 7 u 8 en el anillo de quinazolina, *es decir*, la posición 2 permanece insustituida. Hay que entender además que el grupo R^3, que puede estar presente en el grupo 2,3-metilendioxipiridilo dentro de la Fórmula estructural I, puede localizarse en cualquiera de las dos porciones del anillo de 5 ó 6 miembros, *es decir*, un grupo R^3 puede localizarse en el anillo piridilo o en el grupo metileno dentro del grupo 2,3-metilendioxipiridilo. Por ejemplo, el grupo R^3 puede ser un grupo metilo que se localiza en la porción del grupo metileno del grupo 2,3-metilendioxipiridilo, *es decir*, las posiciones 2 y 3 en el grupo piridilo llevan un grupo etilidendioxi. Preferiblemente, cualquier grupo R^3, que está presente en el grupo 2,3-metilendioxipiridilo dentro de la Fórmula estructural I, se localiza en el anillo piridilo del mismo. Hay que entender además que, cuando están presentes múltiples grupos R^3, los grupos R^3 pueden ser los mismos o diferentes.

Valores apropiados para cualquiera de los grupos 'R' (R^1 a R^{13}) o para varios grupos dentro de un sustituyente R^1 ó R^3 incluyen:-

para halógeno	fluoro, cloro, bromo y yodo;
para (1-8C)alquilo:	metilo, etilo, propilo, isopropilo, tert-butilo, ciclobutilo, ciclopentilo y 2-ciclopropiletilo;
para (1-6C)alquilo:	metilo, etilo, propilo, isopropilo y tert-butilo;

para (2-8C)alquenilo:	vinilo, isopropenilo, alilo y but-2-enilo;
para (2-8C)alquinilo:	etinilo, 2-propinilo y but-2-inilo;
para (1-6C)alcoxi:	metoxi, etoxi, propoxi, isopropoxi y butoxi;
para (2-6C)alqueniloxi:	viniloxi y aliloxi;
para (2-6C)alquiniloxi:	etiniloxi y 2-propiniloxi;
para (1-6C)alquiltio:	metiltio, etiltio y propiltio;
para (1-6C)alquilsulfinilo:	metilsulfinilo y etilsulfinilo;
para (1-6C)alquilsulfonilo:	metilsulfonilo y etilsulfonilo;
para (1-6C)alquilamino:	metilamino, etilamino, propilamino, isopropilamino y butilamino;
para di-[(1-6C)alquil]amino:	dimetilamino, dietilamino, N-etil-N-metilamino y diisopropilamino;
para (1-6C)alcoxicarbonilo:	metoxicarbonilo, etoxicarbonilo, propoxicarbonilo y tert-butoxicarbonilo:
para N-(1-6C)alquilcarbamoilo:	N-metilcarbamoilo, N-etilcarbamoilo y N-propilcarbamoilo;
para N,N-di-[(1-6C)alquil]carbamoilo:	N,N-dimetilcarbamoilo, N-etil-N-metilcarbamoilo y N,N-dietilcarbamoilo;
para (2-6C)alcanoilo:	acetilo, propionilo e isobutirilo;
para (2-6C)alcanoiloxi:	acetoxi y propioniloxi;
para (2-6C)alcanoilamino:	acetamido y propionamido;
para N-(1-6C)alquil-(2-6C)alcanoilamino:	N-metilacetamido y N-metilpropionamido;
para N-(1-6C)alquilsulfamoilo:	N-metilsulfamoilo y N-etilsulfamoilo;
para N,N-di-[(1-6C)alquil]sulfamoilo:	N,N-dimetilsulfamoilo;
para (1-6C)alcanosulfonilamino:	metansulfonilamino y etansulfonilamino;
para N-(1-6C)alquil-(1-6C)alcanosulfonilamino	N-metilmetansulfonilamino y N-metiletansulfonilamino;

para (3-6C)alquenoilamino:	acrilamido, metacrilamido y crotonamido;
para N-(1-6C)alquil-(3-6C)alquenoilamino:	N-metilacrylamido y N-metilcrotonamido;
para (3-6C)alquinoilamino:	propiolamido;
para N-(1-6C)alquil-(3-6C)alquinoilamino:	N-metilpropiolamido;
para amino-(1-6C)alquilo:	aminometilo, 2-aminoetilo, 1-aminoetilo y 3-aminopropilo;
para (1-6C)alquilamino-(1-6C)alquilo:	metilaminometilo, etilaminometilo, 1 metilaminoetilo, 2-metilaminoetilo, 2-etilaminoetilo y 3-metilaminopropilo;
para di-[(1-6C)alquil]amino-(1-6C)alquilo:	dimetilaminometilo, dietilaminometilo, 1-dimetilaminoetilo, 2-dimetilaminoetilo y 3-dimetilaminopropilo;
para halógeno-(1-6C)alquilo:	clorometilo, 2-fluoroetilo, 2-cloroetilo, 1-cloroetilo, 2,2-difluoroetilo, 2,2,2-trifluoroetilo, 3-fluoropropilo, 3-cloropropilo, 3,3-difluoropropilo y 3,3,3-trifluoropropilo;
para hidroxi-(1-6C)alquilo:	hidroximetilo, 2-hidroxietilo, 1-hidroxietilo y 3-hidroxipropilo;
para (1-6C)alcoxi-(1-6C)alquilo:	metoximetilo, etoximetilo, 1-metoxietilo, 2-metoxietilo, 2-etoxietilo y 3-metoxipropilo;
para ciano-(1-6C)alquilo:	cianometilo, 2-cianoetilo, 1-cianoetilo y 3-cianopropilo;
para (2-6C)alcanoilamino-(1-6C)alquilo:	acetamidometilo, propionamidometilo y 2-acetamidoetilo; y
para (1-6C)alcoxicarbonilamino-(1-6C)alquilo:	metoxicarbonilaminometilo, etoxicarbonilaminometilo, tert-butoxicarbonilaminometilo y 2-

metoxicarbonilaminoetilo.

Un valor apropiado de $(R^1)_m$ cuando es un grupo (1-3C)alquilenodioxi o de un grupo (1-3C)alquilenodioxi dentro de un sustituyente R^1 es, por ejemplo, metilendioxi, etilidendioxi, isopropilidendioxi o etilenedioxi y sus átomos de oxígeno ocupan posiciones de anillo adyacentes.

Cuando, como se define anteriormente, un grupo R^1 forma un grupo de la fórmula Q^1-X^1- y, por ejemplo, X^1 es un grupo enlazante $OC(R^4)_2$, es el átomo de carbono, no el átomo de oxígeno, del grupo enlazante $OC(R^4)_2$ el cual se une al anillo de quinazolina y el átomo de oxígeno se une al grupo Q^1. De manera similar, cuando, por ejemplo un grupo CH_3 dentro de un sustituyente R^1 lleva un grupo de la fórmula -X^3-Q^3 y, por ejemplo, X^3 es un grupo enlazante $C(R^7)_2O$, es el átomo de carbono, no el átomo de oxígeno, del grupo enlazante $C(R^7)_2O$, el cual se une al grupo CH_3 y el átomo de oxígeno se enlaza al grupo Q^3. Una convención similar se aplica a la unión de los grupos de las Fórmulas Q^2-X^2- y -X^7-Q^5.

Como se define anteriormente, átomos de carbono adyacentes en cualquier cadena (2-6C)alquileno dentro de un sustituyente R^1 pueden separarse opcionalmente por la inserción en la cadena de un grupo tal como O, $CON(R^5)$ ó C≡C. Por ejemplo, la inserción de un grupo C≡C en la cadena etileno dentro de un grupo 2-morfolinoetoxi da lugar a un grupo 4-morfolinobut-2-iniloxi y, por ejemplo, la inserción de un grupo CONH en la cadena etileno dentro de un grupo 3-metoxipropoxi da lugar, por ejemplo, a un grupo 2-(2-metoxiacetamido)etoxi.

Cuando, como se define anteriormente, cualquier grupo CH_2=CH- ó HC≡C- dentro de un sustituyente R^1 lleva opcionalmente en la posición terminal CH_2= o HC≡ un sustituyente tal como un grupo de la fórmula Q^2-X^2- en donde X^2 es, por ejemplo, NHCO y Q^2 es un grupo heterociclil-(1-6C)alquilo, sustituyentes R^1 apropiados así formados incluyen, por ejemplo, grupos N-[heterociclil-(1-6C)alquil]carbamoilvinilo tales como N-(2-pirrolidin-1-iletil)carbamoilvinilo o grupos N-[heterociclil-(1-6C)alquil]carbamoiletinilo tales como N-(2-pirrolidin-1-

iletil)carbamoiletinilo.

Cuando, como se define anteriormente, cualquier grupo CH_2 o CH_3 dentro de un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 o CH_3 uno o más sustituyentes halógeno o (1-6C)alquilo, hay apropiadamente 1 ó 2 sustituyentes halógeno o (1-6C)alquilo presentes en cada dicho grupo CH_2 y hay apropiadamente 1, 2 ó 3 sustituyentes tales presentes en cada dicho grupo CH_3.

Cuando, como se define anteriormente, cualquier grupo CH_2 o CH_3 dentro de un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 o CH_3 un sustituyente como se define anteriormente, sustituyentes R^1 apropiados así formados incluyen, por ejemplo, grupos heterociclil-(1-6C)alcoxi hidroxi sustituidos, tales como grupos 2-hidroxi-3-piperidinopropoxi y 2-hidroxi-3-morfolinopropoxi, amino-(2-6C)alcoxi hidroxi-sustituidos, tales como grupos 3-amino-2-hidroxipropoxi, (1-6C)alquilamino-(2-6C)alcoxi hidroxi-sustituidos, tales como grupos 2-hidroxi-3-metilaminopropoxi, di-[(1-6C)alquil]amino-(2-6C)alcoxi hidroxi-sustituidos, tales como grupos 3-dimetilamino-2-hidroxipropoxi, heterociclil-(1-6C)alquilamino hidroxi-sustituidos, tales como grupos 2-hidroxi-3-piperidinopropilamino y 2-hidroxi-3-morfolinopropilamino, amino-(2-6C)alquilamino hidroxi-sustituidos, tales como grupos 3-amino-2-hidroxipropilamino, (1-6C)alquilamino-(2-6C)alquilamino hidroxi-sustituidos tales como grupos 2-hidroxi-3-metilaminopropilamino, di-[(1-6C)alquil]amino-(2-6C)alquilamino hidroxi-sustituidos, tales como grupos 3-dimetilamino-2-hidroxipropilamino, (1-6C)alcoxi hidroxi-sustituidos, tales como grupos 2-hidroxietoxi, (1-6C)alcoxi (1-6C)alcoxi-sustituidos tales como grupos 2-metoxietoxi y 3-etoxipropoxi, (1-6C)alcoxi (1-6C)alquilsulfonilo-sustituidos, tales como grupos 2-metilsulfoniletoxi y (1-6C)alquilamino-(1-6C)alquilo heterociclil-sustituido tales como grupos 2-morfolinoetilaminometilo, 2-piperazin-1-iletilaminometilo y 3-morfolinopropilaminometilo.

Hay que entender que cuando, como se define anteriormente, cualquier grupo CH_2 o CH_3 dentro de un sustituyente R^1 lleva

opcionalmente en cada dicho grupo CH_2 o CH_3 un sustituyente como se define anteriormente, tal sustituyente opcional puede estar presente en un grupo CH_2 o CH_3 dentro de los sustituyentes definidos anteriormente, que pueden estar presentes en un grupo arilo, heteroarilo o heterociclilo dentro de un sustituyente R^1. Por ejemplo, si R^1 incluye un grupo arilo o heteroarilo que se sustituye por un grupo (1-8C)alquilo, el grupo (1-8C)alquilo puede sustituirse de manera opcional en un grupo CH_2 o CH_3 allí por uno de sus sustituyentes definidos anteriormente. Por ejemplo, si R^1 incluye un grupo heteroarilo que se sustituye, por ejemplo, por un grupo (1-6C)alquilamino-(1-6C)alquilo, el grupo terminal CH_3 del grupo (1-6C)alquilamino puede sustituirse adicionalmente, por ejemplo, por un grupo (1-6C)alquilsulfonilo o un grupo (2-6C)alcanoilo. Por ejemplo, el grupo R^1 puede ser un grupo heteroarilo tal como un grupo tienilo que se sustituye por un grupo N-(2-metilsulfoniletil)aminometilo de modo que R^1 es, por ejemplo, un grupo 5-[N-(2-metilsulfoniletil)aminometil]tien-2-ilo. Además, por ejemplo, si R^1 incluye un grupo heterociclilo tal como un grupo piperidinilo o piperazinilo, que se sustituye en su átomo de nitrógeno, por ejemplo, por un grupo (2-6C)alcanoilo, el grupo terminal CH_3 del grupo (2-6C)alcanoilo puede sustituirse adicionalmente, por ejemplo, por un grupo di-[(1-6C)alquil]amino. Por ejemplo, el grupo R^1 puede ser un grupo N-(2-dimetilaminoacetil)piperidin-4-ilo o un grupo 4-(2-dimetilaminoacetil)piperazin-1-ilo.

Una sal apropiada farmacéuticamente aceptable de un compuesto de la Fórmula I es, por ejemplo, una sal de adición de ácido de un compuesto de la Fórmula I, por ejemplo una sal de adición de ácido con un ácido orgánico o inorgánico tal como ácido clorhídrico, bromhídrico, sulfúrico, trifluoroacético, cítrico o maleico; o, por ejemplo, una sal de un compuesto de la Fórmula I que es suficientemente ácida, por ejemplo una sal de metal alcalino o alcalinotérreo tal como una sal de calcio o magnesio, o una sal de amonio, o una sal con una base orgánica tal como metilamina, dimetilamina, trimetilamina, piperidina, morfolina o tris-(2-hidroxietil)amina.

Particulares compuestos novedosos de la invención incluyen, por ejemplo, derivados de quinazolina de la Fórmula I, o sus sales farmacéuticamente aceptables, en donde, a menos que se especifique lo contrario, cada uno de Z, m, R^1, n y R^3 tiene cualquiera de los significados definidos anteriormente o en los párrafos (a) a (o) más adelante:-

(a) Z es O, S, SO, SO_2, CH_2 ó NH;

(b) Z es O;-

(c) Z es NH;

(d) m es 1 ó 2, y cada grupo R^1, los cuales pueden ser los mismos o diferentes, se seleccionan de halógeno trifluorometilo, hidroxi, amino, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquilamino, di-[(1-6C)alquil]amino), N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, (3-6C)alquenoilamino, N-(1-6C)alquil-(3-6C)alquenoilamino, (3-6C)alquinoilamino y N-(1-6C)alquil-(3-6C)alquinoilamino, o de un grupo de la fórmula:

$$Q^1\text{-}X^1\text{-}$$

en donde X^1 es un enlace directo o se selecciona de O, $N(R^4)$, $CON(R^4)$, $N(R^4)CO$ y $OC(R^4)_2$ en donde R^4 es hidrógeno o (1-6C)alquilo, y Q^1 es arilo, aril-(1-6C)alquilo, cicloalquil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileno dentro de un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, $N(R^5)$, $CON(R^5)$, $N(R^5)CO$, CH=CH y C≡C en donde R^5 es hidrógeno o (1-6C)alquilo, o, cuando el grupo insertado es $N(R^5)$, R^5 puede ser también (2-6C)alcanoilo,

y en donde cualquier grupo CH_2=CH- o HC≡C- dentro de un sustituyente R^1 lleva opcionalmente en la posición terminal CH_2= o HC≡ un sustituyente seleccionado de carbamoilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo y di-[(1-6C)alquil]amino-(1-6C)alquilo o de un grupo de la

fórmula:

$$Q^2\text{-}X^2\text{-}$$

en donde X^2 es un enlace directo o es CO ó $N(R^6)CO$, en donde R^6 es hidrógeno o (1-6C)alquilo, y Q^2 es heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde cualquier grupo CH_2 o CH_3 dentro de un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 o CH_3 uno o más grupos halógeno o un sustituyente seleccionado de hidroxi, amino, oxo, (1-6C)alcoxi, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (2-6C)alcanoiloxi, (2-6C)alcanoilamino y N-(1-6C)alquil-(2-6C)alcanoilamino, o de un grupo de la fórmula:

$$-X^3\text{-}Q^3$$

en donde X^3 es un enlace directo o se selecciona de O, $N(R^6)$, $CON(R^7)$, $N(R^7)CO$ y $C(R^7)_2O$, en donde R^7 es hidrógeno o (1-6C)alquilo, y Q^3 es heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde cualquier grupo arilo, heteroarilo o heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1, 2 ó 3 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de halógeno trifluorometilo, hidroxi, amino, carbamoilo, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (1-6C)alquilsulfonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo y (1-3C)alquilenodioxi, o lleva opcionalmente 1 sustituyente seleccionado de un grupo de la fórmula:

$$-X^4\text{-}R^8$$

en donde X^4 es un enlace directo o se selecciona de O y $N(R^9)$, en donde R^9 es hidrógeno o (1-6C)alquilo, y R^8 es halógeno-(1-6C)alquilo, hidroxi-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, (2-6C)alcanoilamino-(1-6C)alquilo o (1-6C) alcoxicarbonilamino-(1-6C)alquilo, y de un grupo de la fórmula:

$$-X^5\text{-}Q^4$$

en donde X^5 es un enlace directo o se selecciona de O, $N(R^{10})$ y CO, en donde R^{10} es hidrógeno o (1-6C)alquilo, y Q^4 es heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de halógeno (1-6C)alquilo y (1-6C)alcoxi,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo;

(e) m es 1 ó 2, y cada grupo R^1, los cuales pueden ser los mismos o diferentes, se selecciona de fluoro, cloro, trifluorometilo, hidroxi, amino, carbamoilo, metilo, etilo, propilo, butilo, vinilo, alilo, but-3-enilo, pent-4-enilo, hex-5-enilo, etinilo, 2-propinilo, but-3-inilo, pent-4-inilo, hex-5-inilo, metoxi, etoxi, propoxi, isopropoxi, butoxi, aliloxi, but-3-eniloxi, pent-4-eniloxi, hex-5-eniloxi, etiniloxi, 2-propiniloxi, but-3-iniloxi, pent-4-iniloxi, hex-5-iniloxi, metilamino, etilamino, propilamino, dimetilamino, dietilamino, dipropilamino, N-metilcarbamoilo, N,N-dimetilcarbamoilo, acetamido, propionamido, acrilamido y propiolamido, o de un grupo de la fórmula:

$$Q^1\text{-}X^1\text{-}$$

en donde X^1 es un enlace directo o se selecciona de O, NH, CONH, NHCO y OCH_2 y Q^1 es fenilo, bencilo, ciclopropilmetilo, 2-tienilo, 1-imidazolilo, 1,2,3-triazol-1-ilo, 1,2,4-triazol-1-ilo, 2-, 3- ó 4-piridilo, 2-imidazol-1-iletilo, 3-imidazol-1-ilpropilo, 2-(1,2,3-triazolil)etilo, 3-(1,2,3-triazolil)propilo, 2-(1,2,4-triazolil)etilo, 3-(1,2,4-triazolil)propilo, 2-, 3- ó 4-piridilmetilo, 2-(2-, 3- ó 4-piridil)etilo, 3-(2-, 3- ó 4-piridil)propilo, tetrahidrofuran-3-ilo, 3- ó 4-tetrahidropiranilo, 1-, 2- ó 3-pirrolidinilo, morfolino, 1,1-dioxotetrahidro-4H-1,4-tiazin-4-ilo, piperidino, piperidin-3-ilo, piperidin-4-ilo, 1-, 3- ó 4-homopiperidinilo, piperazin-1-ilo, homopiperazin-1-ilo, 1-, 2- ó 3-pirrolidinilmetilo, morfolinometilo, piperidinometilo, 3- ó 4-piperidinilmetilo, 1-, 3- ó 4-homopiperidinilmetilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-2-ilpropilo, pirrolidin-2-ilmetilo, 2-pirrolidin-2-iletilo, 3-pirrolidin-1-ilpropilo, 4-pirroiidin-1-ilbutilo, 2-morfolinoetilo, 3-morfolinopropilo, 4-morfolinobutilo, 2-(1,1-

dioxotetrahidro-4H-1,4-tiazin-4-il)etilo, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propilo, 2-piperidinoetilo, 3-piperidinopropilo, 4-piperidinobutilo, 2-piperidin-3-iletilo, 3-piperidin-3-ilpropilo, 2-piperidin-4-iletilo, 3-piperidin-4-ilpropilo, 2-homopiperidin-1-iletilo, 3-homopiperidin-1-ilpropilo, 2-(1,2,3,6-tetrahidropiridin-1-il)etilo, 3-(1,2,3,6-tetrahidropiridin-1-il)propilo, 4-(1,2,3,6-tetrahidropiridin-1-il)butil)2-piperazin-1-iletilo, 3-piperazin-1-ilpropilo, 4-piperazin-1-ilbutilo, 2-homopiperazin-1-iletilo o 3-homopiperazin-1-ilpropilo,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileno dentro de un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH, N(Me), CONH, NHCO, CH=CH y C≡C,

y en donde cualquier grupo CH_2=CH- ó HC≡C- dentro de un sustituyente R^1 lleva opcionalmente en la posición terminal CH_2= o HC≡ un sustituyente seleccionado de carbamoilo, N-metilcarbamoilo, N-etilcarbamoilo, N-propilcarbamoilo, N,N-dimetilcarbamoilo, aminometilo, 2-aminoetilo; 3-aminopropilo, 4-aminobutilo, metilaminometilo, 2-metilaminoetilo, 3-metilaminopropilo, 4-metilaminobutilo, dimetilaminometilo, 2-dimetilaminoetilo, 3-dimetilaminopropilo o 4-dimetilaminobutilo, o de un grupo de la fórmula:

$$Q^2\text{-}X^2\text{-}$$

en donde X^2 es un enlace directo o es CO, NHCO ó N(Me)CO y Q^2 es piridilo, piridilmetilo, 2-piridiletilo, pirrolidin-1-ilo, pirrolidin-2-ilo, morfolino, piperidino, piperidin-3-ilo, piperidin-4-ilo, piperazin-1-ilo, pirrolidin-1-ilmetilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, 4-pirrolidin-1-ilbutilo, pirrolidin-2-ilmetilo, 2-pirrolidin-2-iletilo, 3-pirrolidin-2-ilpropilo, morfolinometilo, 2-morfolinoetilo, 3-morfolinopropilo, 4-morfolinobutilo, piperidinometilo, 2-piperidinoetilo, 3-piperidinopropilo, 4-piperidinobutilo, piperidin-3-ilmetilo, 2-piperidin-3-iletilo, piperidin-4-ilmetilo, 2-piperidin-4-iletilo, piperazin-1-ilmetilo, 2-piperazin-1-iletilo, 3-piperazin-1-ilpropilo o 4-piperazin-1-ilbutilo,

y en donde cualquier grupo CH_2 o CH_3 dentro de un sustituyente R^1

lleva opcionalmente en cada dicho grupo CH_2 o CH_3 uno o más grupos fluoro o cloro o un sustituyente seleccionado de hidroxi; amino, oxo, metoxi, metilsulfonilo, metilamino, dimetilamino, diisopropilamino, N-etil-N-metilamino, N-isopropil-N-metilamino, N-metil-N-propilamino, acetoxi, acetamido y N-metilacetamido o de un grupo de la fórmula:

$$-X^3-Q^3$$

en donde X^3 es un enlace directo o se selecciona de O, NH, CONH, NHCO y CH_2O y Q^3 es piridilo, piridilmetilo, pirrolidin-1-ilo, pirrolidin-2-ilo, morfolino, piperidino, piperidin-3-ilo, piperidin-4-ilo, piperazin-1-ilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, pirrolidin-2-ilmetilo, 2-pirrolidin-2-iletilo, 3-pirrolidin-2-ilpropilo, 2-morfolinoetilo, 3-morfolinopropilo, 2-piperidinoetilo, 3-piperidinopropilo, piperidin-3-ilmetilo, 2-piperidin-3-iletilo, piperidin-4-ilmetilo, 2-piperidin-4-iletilo, 2-piperazin-1-iletilo o 3-piperazin-1-ilpropilo,

y en donde cualquier grupo arilo, heteroarilo o heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1, 2 ó 3 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxi, amino, carbamoilo, metilo, etilo, alilo, 2-propinilo, metoxi, metilsulfonilo, N-metilcarbamoilo, N,N-dimetilcarbamoilo, acetilo, propionilo, isobutirilo, metilendioxi, etilidendioxi y isopropilidendioxi, o lleva opcionalmente 1 sustituyente seleccionado de un grupo de la fórmula:

$$-X^4-R^8$$

en donde X^4 es un enlace directo o se selecciona de O y NH y R^8 es 2-fluoroetilo, 2,2-difluoroetilo, 2,2,2-trifluoroetilo, 3-fluoropropilo, 3,3-difluoropropilo, 3,3,3-trifluoropropilo, 2-hidroxietilo, 3-hidroxipropilo, 2-metoxietilo, 3-metoxipropilo, cianometilo, aminometilo, 2-aminoetilo, 3-aminopropilo, metilaminometilo, 2-metilaminoetilo, 3-metilaminopropilo, 2-etilaminoetilo, 3-etilaminopropilo, dimetilaminometilo, 2-dimetilaminoetilo, 3-dimetilaminopropilo, acetamidometilo, metoxicarbonilaminometilo, etoxicarbonilaminometilo o tert-butoxicarbonilaminometilo, y de un grupo de la fórmula:

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

en donde X^5 es un enlace directo o se selecciona de O, NH y CO y Q^4 es pirrolidin-1-ilmetilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, morfolinometilo, 2-morfolinoetilo, 3-morfolinopropilo, piperidinometilo, 2-piperidinoetilo, 3-piperidinopropilo, piperazin-1-ilmetilo, 2-piperazin-1-iletilo o 3-piperazin-1-ilpropilo,cada uno de los cuales lleva opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionado de fluoro, cloro, metilo y metoxi,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo;

(f) m es 1 y el grupo R^1 se localiza en la posición 5, 6 ó 7 o m es 2 y los grupos R^1, los cuales pueden ser los mismos o diferentes, se localizan en las posiciones 5 y 7 o en las posiciones 6 y 7 y cada R^1 se selecciona de hidroxi, amino, metilo, etilo, propilo, butilo, vinilo, etinilo, metoxi, etoxi, propoxi, isopropoxi, butoxi, pentiloxi, but-3-eniloxi, pent-4-eniloxi, hex-5-eniloxi, but-3-iniloxi, pent-4-iniloxi, hex-5-iniloxi, metilamino, etilamino, dimetilamino, dietilamino, acetamido, propionamido, ciclopentiloxi, ciclohexiloxi, fenoxi, benciloxi, tetrahidrofuran-3-iloxi, tetrahidropiran-3-iloxi, tetrahidropiran-4-iloxi, ciclopropilmetoxi, 2-imidazol-1-iletoxi, 3-imidazol-1-ilpropoxi, 2-(1,2,3-triazol-1-il)etoxi, 3-(1,2,3-triazol-1-il)propoxi, 2-(1,2,4-triazol-1-il)etoxi, 3-(1,2,4-triazol-1-il)propoxi, pirid-2-ilmetoxi, pirid-3-ilmetoxi, pirid-4-ilmetoxi, 2-pirid-2-iletoxi, 2-pirid-3-iletoxi, 2-pirid-4-iletoxi, 3-pirid-2-ilpropoxi, 3-pirid-3-ilpropoxi, 3-pirid-4-ilpropoxi, pirrolidin-1-ilo, morfolino, piperidino, piperazin-1-ilo, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 4-pirrolidin-1-ilbutoxi, pirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 2-pirrolidin-2-iletoxi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 4-morfolinobutoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 4-piperidinobutoxi, piperidin-3-iloxi, piperidin-4-iloxi, piperidin-3-ilmetoxi, piperidin-4-ilmetoxi, 2-piperidin-3-iletoxi, 3-piperidin-3-ilpropoxi, 2-piperidin-4-iletoxi, 3-piperidin-4-ilpropoxi, 2-homopiperidin-1-iletoxi, 3-homopiperidin-1-ilpropoxi, 2-(1,2,3,6-tetrahidropiridin-1-il)etoxi 3-

(1,2,3,6-tetrahidropiridin-1-il)propoxi, 4-(1,2,3,6-tetrahidropiridin-1-il)butoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 4-piperazin-1-ilbutoxi, 2-homopiperazin-1-iletoxi, 3-homopiperazin-1-ilpropoxi, 2-pirrolidin-1-iletilamino, 3-pirrolidin-1-ilpropilamino, 4-pirrolidin-1-ilbutilamino, pirrolidin-3-ilamino, pirrolidin-2-ilmetilamino, 2-pirrolidin-2-iletilamino, 3-pirrolidin-2-ilpropilamino, 2-morfolinoetilamino, 3-morfolinopropilamino, 4-morfolinobutilamino, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etilamino, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propilamino, 2-piperidinoetilamino, 3-piperidinopropilamino, 4-piperidinobutilamino, piperidin-3-ilamino, piperidin-4-ilamino, piperidin-3-ilmetilamino, 2-piperidin-3-iletilamino, piperidin-4-ilmetilamino, 2-piperidin-4-iletilamino, 2-homopiperidin-1-iletilamino, 3-homopiperidin-1-ilpropilamino, 2-piperazin-1-iletilamino, 3-piperazin-1-ilpropilamino, 4-piperazin-1-ilbutilamino, 2-homopiperazin-1-iletilamino o 3-homopiperazin-1-ilpropilamino,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileno dentro de un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH, N(Me), CH=CH y C≡C,

y cuando R^1 es un grupo vinilo o etinilo, el sustituyente R^1 lleva opcionalmente en la posición terminal CH_2= o HC≡ un sustituyente seleccionado de N-(2-dimetilaminoetil)carbamoilo, N-(3-dimetilaminopropil)carbamoilo, metilaminometilo, 2-metilaminoetilo, 3-metilaminopropilo, 4-metilaminobutilo, dimetilaminometilo, 2-dimetilaminoetilo, 3-dimetilaminopropilo y 4-dimetilaminobutilo, o de un grupo de la fórmula:

$$Q^2\text{-}X^2\text{-}$$

en donde X^2 es un enlace directo o es NHCO o N(Me)CO y Q^2 es imidazolilmetilo, 2-imidazoliletilo, 3-imidazolilpropilo, piridilmetilo, 2-piridiletilo, 3-piridilpropilo, pirrolidin-1-ilmetilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, 4-pirrolidin-1-ilbutilo, pirrolidin-2-ilmetilo, 2-pirrolidin-2-iletilo, 3-pirrolidin-2-ilpropilo, morfolinometilo, 2-

morfolinoetilo, 3-morfolinopropilo, 4-morfolinobutilo, piperidinometilo, 2-piperidinoetilo, 3-piperidinopropilo, 4-piperidinobutilo, piperidin-3-ilmetilo, 2-piperidin-3-iletilo, piperidin-4-ilmetilo, 2-piperidin-4-iletilo, piperazin-1-ilmetilo, 2-piperazin-1-iletilo, 3-piperazin-1-ilpropilo o 4-piperazin-1-ilbutilo,

y en donde cualquier grupo CH_2 o CH_3 dentro de un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 o CH_3 uno o más grupos fluoro o cloro o un sustituyente seleccionado de hidroxi, oxo, amino, metoxi, metilsulfonilo, metilamino, dimetilamino, diisopropilamino, N-etil-N-metilamino, N-isopropil-N-metilamino, N-metil-N-propilamino, acetoxi, acetamido y N-metilacetamido,

y en donde cualquier grupo fenilo, imidazolilo, triazolilo, piridilo o heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxi, amino, carbamoilo, metilo, etilo, metoxi, etoxi, N-metilcarbamoilo, N,N-dimetilcarbamoilo, metilendioxi, etilidendioxi y isopropilidendioxi, y un grupo pirrolidin-2-ilo, piperidin-3-ilo, piperidin-4-ilo, piperazin-1-ilo o homopiperazin-1-ilo dentro de un sustituyente R^1 se N-sustituye opcionalmente con alilo, 2-propinilo, metilsulfonilo, etilsulfonilo, acetilo, propionilo, isobutirilo, 2-fluoroetilo, 2,2-difluoroetilo, 2,2,2-trifluoroetilo, 3-fluoropropilo, 3,3-difluoropropilo, 3,3,3-trifluoropropilo, 2-metoxietilo, 3-metoxipropilo, cianometilo, 2-aminoetilo, 3-aminopropilo, 2-metilaminoetilo, 3-metilaminopropilo, 2-dimetilaminoetilo, 3-dimetilaminopropilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, 2-morfolinoetilo, 3-morfolinopropilo, 2-piperidinoetilo, 3-piperidinopropilo, 2-piperazin-1-iletilo o 3-piperazin-1-ilpropilo, cuyos últimos 8 sustituyentes lleva cada uno opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, metilo y metoxi,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo;

(g) m es 1 y el grupo R^1 se localiza en la posición 7 ó m es 2 y los grupos

R^1, los cuales pueden ser los mismos o diferentes, se localizan en las posiciones 6 y 7 y cada R^1 se selecciona de hidroxi, amino, metilo, etilo, metoxi, etoxi, propoxi, isopropoxi, butoxi, metilamino, etilamina, dimetilamino, dietilamino, acetamido, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 4-pirrolidin-1-ilbutoxi, pirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 2-pirroridin-2-iletoxi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 4-morfolinobutoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 4-piperidinobutoxi, piperidin-3-iloxi, piperidin-4-iloxi, piperidin-3-ilmetoxi, 2-piperidin-3-iletoxi, piperidin-4-ilmetoxi, 2-piperidin-4-iletoxi, 2-homopiperidin-1-iletoxi, 3-homopiperidin-1-ilpropoxi, 3-(1,2,3,6-tetrahidropiridin-1-il)propoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-homopiperazin-1-iletoxi y 3-homopiperazin-1-ilpropoxi,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileno dentro de un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH, CH=CH y C≡C,

y en donde cualquier grupo CH_2 o CH_3 dentro de un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 o CH_3 uno o más grupos cloro o un sustituyente seleccionado de hidroxi, oxo, amino, metoxi, metilsulfonilo, metilamino, dimetilamino, diisopropilamino, N-etil-N-metilamino, N-isopropil-N-metilamino y acetoxi,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxi, amino, metilo, etilo, metoxi, metilendioxi, etilidendioxi y isopropilidendioxi, y un grupo pirrolidin-2-ilo, pirrolidin-3-ilo, piperidin-3-ilo, piperidin-4-ilo, piperazin-1-ilo u homopiperazin-1-ilo dentro de un sustituyente R^1 se N-sustituye opcionalmente con metilo, etilo, propilo, alilo, 2-propinilo, metilsulfonilo, acetilo, propionilo, isobutirilo, 2-fluoroetilo, 2,2-difluoroetilo, 2,2,2-trifluoroetilo o cianometilo,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en

R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo;

(h) m es 1 y el grupo R^1 se localiza en la posición 5 ó m es 2 y los grupos R^1, los cuales pueden ser los mismos o diferentes, se localizan en las posiciones 5 y 7 y cada R^1 se selecciona de hidroxi, amino, metilo, etilo, metoxi, etoxi, propoxi, isopropoxi, butoxi, metilamino, etilamino, dimetilamino, dietilamino, acetamido, tetrahidrofuran-3-iloxi, tetrahidropiran-4-iloxi, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 4-pirrolidin-1-ilbutoxi, pirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 2-pirrolidin-2-iletoxi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 4-morfolinobutoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 4-piperidinobutoxi, 3-piperidiniloxi, 4-piperidiniloxi, piperidin-3-ilmetoxi, piperidin-4-ilmetoxi, 2-piperidin-3-iletoxi, 2-piperidin-4-iletoxi, 2-homopiperidin-1-iletoxi, 3-homopiperidin-1-ilpropoxi, 3-(1,2,3,6-tetrahidropiridin-1-il)propoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-homopiperazin-1-iletoxi, 3-homopiperazin-1-ilpropoxi, ciclobutiloxi, ciclopentiloxi y ciclohexiloxi,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileno dentro de un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH, CH=CH y C≡C,

y en donde cualquier grupo CH_2 o CH_3 dentro de un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 o CH_3 uno o más grupos cloro o un sustituyente seleccionado de hidroxi, oxo, amino, metoxi, metilsulfonilo, metilamino, dimetilamino, diisopropilamino, N-etil-N-metilamino, N-isopropil-N-metilamino y acetoxi,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxi, amino, metilo, etilo, metoxi, metilendioxi, etilidendioxi y isopropilidendioxi, y un grupo pirrolidin-2-ilo, pirrolidin-3-ilo, piperidin-3-ilo, piperidin-4-ilo, piperazin-1-ilo u homopiperazin-1-ilo dentro de un sustituyente R^1 se N-sustituye opcionalmente con metilo, etilo, propilo,

alilo, 2-propinilo, metilsulfonilo, acetilo, propionilo, isobutirilo, 2-fluoroetilo, 2,2-difluoroetilo, 2,2,2-trifluoroetilo o cianometilo,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo;

(i) m es 2 y los grupos R^1, los cuales pueden ser los mismos o diferentes, se localizan en las posiciones 6 y 7 y el grupo R^1 en la posición 6 se selecciona de hidroxi, metoxi, etoxi y propoxi, y el grupo R^1 en la posición 7 se selecciona de metoxi, etoxi, propoxi, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi,4-pirrolidin-1-ilbutoxi, pirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 2-pirrolidin-2-iletoxi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 4-morfolinobutoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 4-piperidinobutoxi, piperidin-3-iloxi, piperidin-4-iloxi, piperidin-3-ilmetoxi, 2-piperidin-3-iletoxi, piperidin-4-ilmetoxi, 2-piperidin-4-iletoxi, 2-homopiperidin-1-iletoxi, 3-homopiperidin-1-ilpropoxi, 3-(1,2,3,6-tetrahidropiridin-1-il)propoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-homopiperazin-1-iletoxi y 3-homopiperazin-1-ilpropoxi,

y en donde, cualquier grupo CH_2 o CH_3 dentro de un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 o CH_3 uno o más grupos cloro o un sustituyente seleccionado de hidroxi, oxo, amino, metoxi, metilsulfonilo, metilamino, dimetilamino, diisopropilamino, N-etil-N-metilamino, N-isopropil-N-metilamino y acetoxi,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxi, amino, metilo, etilo, metoxi, metilendioxi, etilidendioxi e isopropilidendioxi, y un grupo pirrolidin-2-ilo, pirrolidin-3-ilo, piperidin-3-ilo, piperidin-4-ilo, piperazin-1-ilo o homopiperazin-1-ilo dentro de un sustituyente R^1 se N-sustituye opcionalmente con metilo, etilo, propilo, alilo, 2-propinilo, metilsulfonilo, acetilo, propionilo, isobutirilo, 2-fluoroetilo, 2,2-difluoroetilo, 2,2,2-trifluoroetilo o cianometilo,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo;

(j) m es 2 y los grupos R^1, los cuales pueden ser los mismos o diferentes, se localizan en las posiciones 5 y 7 y el grupo R^1 en la posición 5 se selecciona de metoxi, etoxi, propoxi, isopropoxi, butoxi, tetrahidrofuran-3-iloxi, tetrahidropiran-4-iloxi, pirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 3-piperidiniloxi, 4-piperidiniloxi, piperidin-3-ilmetoxi, piperidin-4-ilmetoxi, ciclobutiloxi, ciclopentiloxi y ciclohexiloxi, y el grupo R^1 en la posición 7 se selecciona de hidroxi, metoxi, etoxi, propoxi, isopropoxi, butoxi, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 4-pirrolidin-1-ilbutoxi, 2-pirrolidin-2-iletoxi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 4-morfolinobutoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 4-piperidinobutoxi, 2-piperidin-3-iletoxi, 2-piperidin-4-iletoxi, 2-homopiperidin-1-iletoxi, 3-homopiperidin-1-ilpropoxi, 3-(1,2,3,6-tetrahidropiridin-1-il)propoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-homopiperazin-1-iletoxi y 3-homopiperazin-1-ilpropoxi,

y en donde cualquier grupo CH_2 o CH_3 dentro de un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 o CH_3 uno o más grupos cloro o un sustituyente seleccionado de hidroxi, oxo, amino, metoxi, metilsulfonilo, metilamino, dimetilamino, diisopropilamino, N-etil-N-metilamino, N-isopropil-N-metilamino y acetoxi,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxi, amino, metilo, etilo, metoxi, metilendioxi, etilidendioxi y isopropilidendioxi, y un grupo pirrolidin-2-ilo, pirrolidin-3-ilo, piperidin 3-ilo, piperidin-4-ilo, piperazin-1-ilo o homopiperazin-1-ilo dentro de un sustituyente R^1 se N-sustituye opcionalmente con metilo, etilo, propilo, alilo, 2-propinilo, metilsulfonilo, acetilo, propionilo, isobutirilo, 2-fluoroetilo, 2,2-difluoroetilo, 2,2,2-trifluoroetilo o cianometilo,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo;

(k) n es 0;

(l) n es 1 ó 2 y los grupos R^3, los cuales pueden ser los mismos o diferentes, se localizan en las posiciones 5 y/o 6 del grupo 2,3-metilendioxipiridin-4-ilo y se seleccionan de halógeno trifluorometilo, ciano; hidroxi, (1-6C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo y (1-6C)alcoxi;

(m) n es 1 ó 2 y los grupos R^3, los cuales pueden ser los mismos o diferentes, se localizan en las posiciones 5 y/o 6 del grupo 2,3-metilendioxipiridin-4-ilo y se seleccionan de fluoro, cloro, bromo, yodo, trifluorometilo, ciano, hidroxi, metilo, etilo, vinilo, alilo, isopropenilo, etinilo, 1-propinilo, 2-propinilo, metoxi y etoxi;

(n) n es 0 ó n es 1 y el grupo R^3 se localiza en la posición 5 ó 6 del grupo 2,3-metilendioxipiridin-4-ilo, especialmente la posición 5, y se selecciona de fluoro, cloro, bromo, trifluorometilo, ciano, hidroxi, metilo, etilo, metoxi y etoxi; y

(o) n es 1 y el grupo R^3 se localiza en la posición 5 del grupo 2,3-metilendioxipiridin-4-ilo y se selecciona de fluoro, cloro, bromo, trifluorometilo, ciano, hidroxi, metilo, etilo, metoxi y etoxi.

Otros compuestos novedosos particulares de la invención incluyen, por ejemplo, derivados de quinazolina de la Fórmula I, o sus sales farmacéuticamente aceptables, en donde, a menos que se especifique lo contrario, cada uno de Z, m, R^1, n y R^3 tiene cualquiera de los significados definidos anteriormente, con la condición que:-

(A) sustituyentes R^1 pueden localizarse únicamente en las posiciones 5, 6 y/o 7 en el anillo de quinazolina *i.e.* las posiciones 2 y 8 permanecen no sustituidos; o

(B) sustituyentes R^1 pueden localizarse únicamente en las posiciones 6 y/o 7 en el anillo de quinazolina *i.e.* las posiciones 2, 5 y 8 permanecen no sustituidos.

Un compuesto particular de la invención es un derivado de

quinazolina de la Fórmula I en donde:

Z es O ó NH;

m es 1 y el grupo R^1 se localiza en la posición 5, 6 ó 7 ó m es 2 y los grupos R^1, los cuales pueden ser los mismos o diferentes, se localizan en las posiciones 5 y 7 o en las posiciones 6 y 7 y cada R^1 se selecciona de hidroxi, amino, metilo, etilo, propilo, butilo, vinilo, etinilo, metoxi, etoxi, propoxi, isopropoxi, butoxi, pentiloxi, but-3-eniloxi, pent-4-eniloxi, hex-5-eniloxi, but-3-iniloxi, pent-4-iniloxi, hex-5-iniloxi, metilamino, etilamino, dimetilamino, dietilamino, acetamido, propionamido, ciclopentiloxi, ciclohexiloxi, fenoxi, benciloxi, tetrahidrofuran-3-iloxi, tetrahidropiran-3-iloxi, tetrahidropiran-4-iloxi, ciclopropilmetoxi, 2-imidazol-1-iletoxi, 3-imidazol-1-ilpropoxi, 2-(1,2,3-triazol-1-il)etoxi, 3-(1,2,3-triazol-1-il)propoxi, 2-(1,2,4-triazol-1-il)etoxi, 3(1,2,4-triazol-1-il)propoxi, pirid-2-ilmetoxi, pirid-3-ilmetoxi, pirid-4-ilmetoxi, 2-pirid-2-iletoxi, 2-pirid-3-iletoxi, 2-pirid-4-iletoxi, 3-pirid-2-ilpropoxi, 3-pirid-3-ilpropoxi, 3-pirid-4-ilpropoxi, pirrolidin-1-ilo, morfolino, piperidino, piperazin-1-ilo, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 4-pirrolidin-1-ilbutoxi, pirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 2-pirrolidin-2-iletoxi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 4-morfolinbutoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 4-piperidinobutoxi, piperidin-3-iloxi, piperidin-4-iloxi, piperidin-3-ilmetoxi, piperidin-4-ilmetoxi, 2-piperidin-3-iletoxi, 3-piperidin-3-ilpropoxi, 2-piperidin-4-iletoxi,3-piperidin-4-ilpropoxi, 2-homopiperidin-1-iletoxi, 3-homopiperidin-1-ilpropoxi, 2-(1,2,3,6-tetrahidropiridin-1-il)etoxi 3-(1,2,3,6-tetrahidropiridin-1-il)propoxi, 4-(1,2,3,6-tetrahidropiridin-1-il)butoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 4-piperazin-1-ilbutoxi, 2-homopiperazin-1-iletoxi, 3-homopiperazin-1-ilpropoxi, 2-pirrolidin-1-iletilamino, 3-pirrolidin-1-ilpropilamino, 4-pirrolidin-1-ilbutilamino, pirrolidin-3-ilamino, pirrolidin-2-ilmetilamino, 2-pirrolidin-2-iletilamino, 3-pirrolidin-2-ilpropilamino, 2-morfolinoetilamino, 3-morfolinopropilamino, 4-morfolinobutilamino, 2-(1,1-dioxotetrahidro-4H-

1,4-tiazin-4-il)etilamino, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propilamino, 2-piperidinoetilamino, 3-piperidinopropilamino, 4-piperidinobutilamino, piperidin-3-ilamino, piperidin-4-ilamino, piperidin-3-ilmetilamino, 2-piperidin-3-iletilamino, piperidin-4-ilmetilamino, 2-piperidin-4-iletilamino, 2-homopiperidin-1-iletilamino, 3-homopiperidin-1-ilpropilamino, 2-piperazin-1-iletilamino, 3-piperazin-1-ilpropilamino, 4-piperazin-1-ilbutilamino, 2-homopiperazin-1-iletilamino o 3-homopiperazin-1-ilpropilamino,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileno dentro de un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH, N(Me), CH=CH y C≡C,

y cuando R^1 es un grupo vinilo o etinilo, el sustituyente R^1 lleva opcionalmente en la posición terminal CH_2= o HC≡ un sustituyente seleccionado de N-(2-dimetilaminoetil)carbamoilo, N-(3-dimetilaminopropil)carbamoilo, metilaminometilo, 2-metilaminoetilo, 3-metilaminopropilo, 4-metilaminobutilo, dimetilaminometilo, 2-dimetilaminoetilo, 3-dimetilaminopropilo y 4-dimetilaminobutilo, o de un grupo de la fórmula.

$$Q^2\text{-}X^2\text{-}$$

en donde X^2 es un enlace directo o es NHCO o N(Me)CO y Q^2 es imidazolilmetilo, 2-imidazoliletilo, 3-imidazolilpropilo, piridilmetilo, 2-piridiletilo, 3-piridilpropilo, pirrolidin-1-ilmetilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, 4-pirrolidin-1-ilbutilo, pirrolidin-2-ilmetilo, 2-pirrolidin-2-iletilo, 3-pirrolidin-2-ilpropilo, morfolinometilo, 2-morfolinoetilo, 3-morfolinopropilo, 4-morfolinobutilo, piperidinometilo, 2-piperidinoetilo, 3-piperidinopropilo, 4-piperidinobutilo, piperidin-3-ilmetilo, 2-piperidin-3-iletilo, piperidin-4-ilmetilo, 2-piperidin-4-iletilo, piperazin-1-ilmetilo, 2-piperazin-1-iletilo, 3-piperazin-1-ilpropilo ó 4-piperazin-1-ilbutilo,

y en donde cualquier grupo CH_2 o CH_3 dentro de un sustituyente R^1

lleva opcionalmente en cada dicho grupo CH_2 o CH_3 uno o más grupos fluoro o cloro o un sustituyente seleccionado de hidroxi, oxo, amino, metoxi, metilsulfonilo, metilamino, dimetilamino, diisopropilamino, N-etil-N-metilamino, N-isopropil-H-metilamino, N-metil-N-propilamino, acetoxi, acetamido y N-metilacetamido,

y en donde cualquier grupo fenilo, imidazolilo, triazolilo, piridilo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxi, amino, carbamoilo, metilo, etilo, metoxi, etoxi, N-metilcarbamoilo, N,N-dimetilcarbamoilo, metilendioxi, etilidendioxi y isopropilidendioxi, y un grupo pirrolidin-2-ilo, piperidin-3-ilo, piperidin-4-ilo, piperazin-1-ilo u homopiperazin-1-ilo dentro de un sustituyente R^1 se N-sustituye opcionalmente con alilo, 2-propinilo, metilsulfonilo, etilsulfonilo, acetilo, propionilo, isobutirilo, 2-fluoroetilo, 2,2-difluoroetilo, 2,2,2-trifluoroetilo, 3-fluoropropilo, 3,3-difluoropropilo, 3,3,3-trifluoropropilo, 2-metoxietilo, 3-metoxipropilo, cianometilo, 2-aminoetilo, 3-aminopropilo, 2-metilaminoetilo, 3-metilaminopropilo, 2-dimetilaminoetilo, 3-dimetilaminopropilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, 2-morfolinoetilo, 3-morfolinopropilo, 2-piperidinoetilo, 3-piperidinopropilo, 2-piperazin-1-iletilo ó 3-piperazin-1-ilpropilo, cuyos últimos 8 sustituyentes lleva cada uno opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, metilo y metoxi,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo;

n es 0 ó n es 1 y el grupo R^3 se localiza en la posición 5 ó 6 del grupo 2,3-metilendioxipiridin-4-ilo y se selecciona de fluoro, cloro, bromo, trifluorometilo, ciano, hidroxi, metilo, etilo, metoxi y etoxi;

o su sal de adición de ácido farmacéuticamente aceptable.

Un compuesto particular adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

Z es NH;

m es 2 y los grupos R^1, los cuales pueden ser los mismos o diferentes, se localizan en las posiciones 6 y 7 y el grupo R^1 en la posición 6 se selecciona de hidroxi, metoxi, etoxi y propoxi, y el grupo R^1 en la posición 7 se selecciona de metoxi, etoxi, propoxi, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 4-pirrolidin-1-ilbutoxi, pirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 2-pirrolidin-2-iletoxi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 4-morfolinobutoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 4-piperidinobutoxi, piperidin-3-iloxi, piperidin-4-iloxi, piperidin-3-ilmetoxi, 2-piperidin-3-iletoxi, piperidin-4-ilmetoxi, 2-piperidin-4-iletoxi, 2-homopiperidin-1-iletoxi, 3-homopiperidin-1-ilpropoxi, 3-(1,2,3,6-tetrahidropiridin-1-il)propoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-homopiperazin-1-iletoxi y 3-homopiperazin-1-ilpropoxi,

y en donde cualquier grupo CH_2 o CH_3 dentro de un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 o CH_3 uno o más grupos cloro o un sustituyente seleccionado de hidroxi, oxo, amino, metoxi, metilsulfonilo, metilamino, dimetilamino, diisopropilamino, N-etil-N-metilamino, N-isopropil-N-metilamino y acetoxi,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxi, amino, metilo, etilo, metoxi, metilendioxi, etilidendioxi y isopropilidendioxi, y un grupo pirrolidin-2-ilo, pirrolidin-3-ilo, piperidin-3-ilo, piperidin-4-ilo, 5 piperazin-1-ilo u homopiperazin-1-ilo dentro de un sustituyente R^1 se N-sustituye opcionalmente con metilo, etilo, propilo, alilo, 2-propinilo, metilsulfonilo, acetilo, propionilo, isobutirilo, 2-fluoroetilo, 2,2-difluoroetilo, 2,2,2-trifluoroetilo o cianometilo,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo;

n es 0 ó n es 1 y el grupo R^3 se localiza en la posición 5 ó 6 del grupo 2,3-metilendioxipiridin-4-ilo y se selecciona de cloro, bromo,

trifluorometilo, ciano, hidroxi, metilo, etilo, metoxi y etoxi;
o su sal de adición de ácido farmacéuticamente aceptable.

Un compuesto particular adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

Z es NH;

m es 2 y el primer grupo R^1 es un grupo 6-metoxi y el segundo grupo R^1 se localiza en la posición 7 y se selecciona de 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]etoxi, 3-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]propoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-piperidin-3-iletoxi, 2-(N-metilpiperidin-3-il)etoxi, 3-piperidin-3-ilpropoxi, 3-(N-metilpiperidin-3-il)propoxi, 2-piperidin-4-iletoxi, 2-(N-metilpiperidin-4-il)etoxi, 3-piperidin-4-ilpropoxi, 3-(N-metilpiperidin-4-il)propoxi, 2-(1,2,3,6-tetrahidropiridin-1-il)etoxi, 3-(1,2,3,6-tetrahidropiridin-1-il)propoxi, 2-(4-hidroxipiperidin-1-il)etoxi, 3-(4-hidroxipiperidin-1-il)propoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 4-piperazin-1-ilbutoxi, 2-(4-metilpiperazin-1-il)etoxi, 3-(4-metilpiperazin-1-il)propoxi, 4-(4-metilpiperazin-1-il)butoxi, 2-(4-alilpiperazin-1-il)etoxi, 3-(4-alilpiperazin-1-il)propoxi, 2-(4-prop-2-inilpiperazin-1-il)etoxi, 3-(4-prop-2-inilpiperazin-1-il)propoxi, 2-(4-metilsulfonilpiperazin-1-il)etoxi, 3-(4-metilsulfonilpiperazin-1-il)propoxi, 2-(4-acetilpiperazin-1-il)etoxi, 3-(4-acetilpiperazin-1-il)propoxi, 4-(4-acetilpiperazin-1-il)butoxi, 2-(4-isobutirilpiperazin-1-il)etoxi, 3-(4-isobutirilpiperazin-1-il)propoxi, 4-(4-isobutirilpiperazin-1-il)butoxi, 2-[4-(2-fluoroetil)piperazin-1-il]etoxi, 3-[4-(2-fluoroetil)piperazin-1-il]propoxi, 2-[4-(2,2,2-trifluoroetil)piperazin-1-il]etoxi, 3-[4-(2,2,2-trifluoroetil)piperazin-1-il]propoxi, 2-(4-cianometilpiperazin-1-il)etoxi, 3-(4-cianometilpiperazin-1-il)propoxi, 2-[2-(4-metilpiperazin-1-il)etoxi]etoxi, 2-cloroetoxi, 3-cloropropoxi, 4-clorobutoxi, 2-metilsulfoniletoxi, 3-metilsulfonilpropoxi, 2-(2-metoxietoxi)etoxi, 2-(4-piridiloxi)etoxi, 3-piridilmetoxi y 2-cianopirid-4-ilmetoxi; y

n es 0 ó n es 1 y el grupo R^3 se localiza en la posición 5 ó 6 del grupo 2,3-metilendioxipiridin-4-ilo y se selecciona de fluoro, cloro, bromo, trifluorometilo y ciano;
o su sal de adición de ácido farmacéuticamente aceptable.

Un compuesto particular adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

Z es NH;

m es 2 y el primer grupo R^1 es un grupo 6-metoxi y el segundo grupo R^1 se localiza en la posición 7 y se selecciona de 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]etoxi, 3-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]propoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-(4-metilpiperazin-1-il)etoxi, 3-(4-metilpiperazin-1-il)propoxi, 2-(4-alilpiperazin-1-il)etoxi, 3-(4-alilpiperazin-1-il)propoxi, 2-(4-prop-2-inilpiperazin-1-il)etoxi, 3-(4-prop-2-inilpiperazin-1-il)propoxi, 2-(4-acetilpiperazin-1-il)etoxi, 3-(4-acetilpiperazin-1-il)propoxi, 2-(4-isobutirilpiperazin-1-il)etoxi, 3-(4-isobutirilpiperazin-1-il)propoxi, 2-[4-(2,2,2-trifluoroetil)piperazin-1-il]etoxi y 3-[4-(2,2,2-trifluoroetil) piperazin-1-il]propoxi; y

n es 1 y el grupo R^3 se localiza en la posición 6 del grupo 2,3-metilendioxipiridin-4-ilo y se selecciona de cloro y bromo;
o su sal de adición de ácido farmacéuticamente aceptable.

Un compuesto particular adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

Z es NH;

m es 2 y los grupos R^1, los cuales pueden ser los mismos o diferentes, se localizan en las posiciones 5 y 7 y el grupo R^1 en la posición 5 se selecciona de metoxi, etoxi, propoxi, isopropoxi, butoxi, tetrahidrofuran-3-iloxi, tetrahidropiran-4-iloxi, pirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 3-piperidiniloxi, 4-piperidiniloxi, piperidin-3-ilmetoxi, piperidin-4-ilmetoxi, ciclobutiloxi, ciclopentiloxi y ciclohexiloxi, y el grupo R^1 en la posición 7 se selecciona de hidroxi, metoxi, etoxi, propoxi, isopropoxi, butoxi, 2-

pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 4-pirrolidin-1-ilbutoxi, 2-pirrolidin-2-iletoxi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 4-morfolinobutoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 4-piperidinobutoxi, 2-piperidin-3-iletoxi, 2-piperidin-4-iletoxi, 2-homopiperidin-1-iletoxi, 3-homopiperidin-1-ilpropoxi, 3-(1,2,3,6-tetrahidropiridin-1-il)propoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-homopiperazin-1-iletoxi y 3-homopiperazin-1-ilpropoxi,

y en donde cualquier grupo CH_2 o CH_3 dentro de un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 o CH_3 uno o más grupos cloro o un sustituyente seleccionado de hidroxi, oxo, amino, metoxi, metilsulfonilo, metilamino, dimetilamino, diisopropilamino, N-etil-N-metilamino, N-isopropil-N-metilamino y acetoxi,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxi, amino, metilo, etilo, metoxi, metilendioxi, etilidendioxi y isopropilidendioxi, y un grupo pirrolidin-2-ilo, pirrolidin-3-ilo, piperidin-3-ilo, piperidin-4-ilo, piperazin-1-ilo u homopiperazin-1-ilo dentro de un sustituyente R^1 se N-sustituye opcionalmente con metilo, etilo, propilo, alilo, 2-propinilo, metilsulfonilo, acetilo, propionilo, isobutirilo, 2-fluoroetilo, 2,2-difluoroetilo, 2,2,2-trifluoroetilo o cianometilo,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo;

n es 0 ó n es 1 y el grupo R^3 se localiza en la posición 5 ó 6 del grupo 2,3-metilendioxipiridin-4-ilo y se selecciona de fluoro, cloro, bromo, trifluorometilo, ciano, hidroxi, metilo, etilo, metoxi y etoxi; o su sal de adición de ácido farmacéuticamente aceptable.

Un compuesto particular adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

Z es NH;

m es 1 y el grupo R^1 se localiza en la posición 5 y se selecciona de etoxi, propoxi, isopropoxi, butoxi, tetrahidrofuran-3-iloxi, tetrahidropiran-4-iloxi, tetrahidrotien-3-iloxi, 1,1-dioxotetrahidrotien-3-iloxi, tetrahidrotiopiran-4-iloxi, 1,1-dioxotetrahidrotiopiran-4-iloxi, N-metilazetidin-3-iloxi, N-etilazetidin-3-iloxi, N-isopropilazetidin-3-iloxi, pirrolidin-3-iloxi, N-metilpirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 3-piperidiniloxi, N-metilpiperidin-3-iloxi, 4-piperidiniloxi, N-metilpiperidin-4-iloxi, N-alilpiperidin-4-iloxi, N-prop-2-inilpiperidin-4-iloxi, N-acetilpiperidin-4-iloxi, N-metilsulfonilpiperidin-4-iloxi, N-(2-metoxietil)piperidin-4-iloxi, piperidin-3-ilmetoxi, N-metilpiperidin-3-ilmetoxi, piperidin-4-ilmetoxi, N-metilpiperidin-4-ilmetoxi, ciclobutiloxi, ciclopentiloxi y ciclohexiloxi,

o m es 2 y el primer grupo R^1 se localiza en la posición 5 y se selecciona del grupo de sustituyentes listado inmediatamente arriba y el segundo grupo R^1 se localiza en la posición 7 y se selecciona de 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]etoxi, 3-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]propoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-piperidin-3-iletoxi, 2-(N-metilpiperidin-3-il)etoxi, 3-piperidin-3-ilpropoxi, 3-(N-metilpiperidin-3-il)propoxi, 2-piperidin-4-iletoxi, 2-(N-metilpiperidin-4-il)etoxi, 3-piperidin-4-ilpropoxi, 3-(N-metilpiperidin-4-il)propoxi, 2-(1,2,3,6-tetrahidropiridin-1-il)etoxi, 3-(1,2,3,6-tetrahidropiridin-1-il)propoxi, 2-(4-hidroxipiperidin-1-il)etoxi, 3-(4-hidroxipiperidin-1-il)propoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 4-piperazin-1-ilbutoxi, 2-(4-metilpiperazin-1-il)etoxi, 3-(4-metilpiperazin-1-il)propoxi, 4-(4-metilpiperazin-1-il)butoxi, 2-(4-alilpiperazin-1-il)etoxi, 3-(4-alilpiperazin-1-il)propoxi, 2-(4-prop-2-inilpiperazin-1-il)etoxi, 3-(4-prop-2-inilpiperazin-1-il)propoxi, 2-(4-metilsulfonilpiperazin-1-il)etoxi, 3-(4-metilsulfonilpiperazin-1-il)propoxi, 2-(4-acetilpiperazin-1-il)etoxi, 3-(4-acetilpiperazin-1-il)propoxi, 4-(4-acetilpiperazin-1-il)butoxi, 2-(4-isobutirilpiperazin-1-il)etoxi, 3-(4-

isobutirilpiperazin-1-il)propoxi, 4-(4-isobutirilpiperazin-1-il)butoxi, 2-[4-(2-fluoroetil)piperazin-1-il]etoxi, 3-[4-(2-fluoroetil)piperazin-1-il]propoxi, 2-[4-(2,2,2-trifluoroetil)piperazin-1-il]etoxi, 3-[4-(2,2,2-trifluoroetil) piperazin-1-il]propoxi, 2-(4-cianometilpiperazin-1-il)etoxi, 3-(4-cianometilpiperazin-1-il)propoxi, 2-[2-(4-metilpiperazin-1-il)etoxi]etoxi, 2-cloroetoxi, 3-cloropropoxi, 4-clorobutoxi, 2-metilsulfoniletoxi, 3-metilsulfonilpropoxi, 2-(2-metoxietoxi)etoxi, 2-(4-piridiloxi)etoxi, 3-piridilmetoxi y 2-cianopirid-4-ilmetoxi;

n es 0 ó n es 1 y el grupo R^3 se localiza en la posición 5 ó 6 del grupo 2,3-metilendioxipiridin-4-ilo y se selecciona de cloro, bromo, trifluorometilo, ciano, hidroxi, metilo, etilo, metoxi y etoxi; o su sal de adición de ácido farmacéuticamente aceptable.

Un compuesto particular adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

Z es NH;

m es 1 y el grupo R^1 se localiza en la posición 5 y se selecciona de propoxi, isopropoxi, tetrahidrofuran-3-iloxi, tetrahidropiran-4-iloxi, pirrolidin-3-iloxi, N-metilpirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 3-piperidiniloxi, N-metilpiperidin-3-iloxi, 4-piperidiniloxi, N-metilpiperidin-4-iloxi, N-alilpiperidin-4-iloxi, N-prop-2-inilpiperidin-4-iloxi, N-acetilpiperidin-4-iloxi, N-metilsulfonilpiperidin-4-iloxi, piperidin-3-ilmetoxi, N-metilpiperidin-3-ilmetoxi, piperidin-4-ilmetoxi, N-metilpiperidin-4-ilmetoxi, ciclobutiloxi, ciclopentiloxi y ciclohexiloxi,

o m es 2 y el primer grupo R^1 se localiza en la posición 5 y se selecciona del grupo de sustituyentes listado inmediatamente arriba y el segundo grupo R^1 se localiza en la posición 7 y se selecciona de 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]etoxi, 3-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]propoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-piperidin-3-iletoxi, 2-(N-metilpiperidin-3-il)etoxi, 3-piperidin-3-ilpropoxi, 3-(N-metilpiperidin-3-

il)propoxi, 2-piperidin-4-iletoxi, 2-(N-metilpiperidin-4-il)etoxi, 3-piperidin-4-ilpropoxi, 3-(N-metilpiperidin-4-il)propoxi, 2-(1,2,3,6-tetrahidropiridin-1-il)etoxi, 3-(1,2,3,6-tetrahidropiridin-1-il)propoxi, 2-(4-hidroxipiperidin-1-il)etoxi, 3-(4-hidroxipiperidin-1-il)propoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 4-piperazin-1-ilbutoxi, 2-(4-metilpiperazin-1-il)etoxi, 3-(4-metilpiperazin-1-il)propoxi, 4-(4-metilpiperazin-1-il)butoxi, 2-(4-alilpiperazin-1-il)etoxi, 3-(4-alilpiperazin-1-il)propoxi, 2-(4-prop-2-inilpiperazin-1-il)etoxi, 3-(4-prop-2-inilpiperazin-1-il)propoxi, 2-(4-metilsulfonilpiperazin-1-il) etoxi, 3-(4-metilsulfonilpiperazin-1-il)propoxi, 2-(4-acetilpiperazin-1-il)etoxi, 3-(4-acetilpiperazin-1-il)propoxi, 4-(4-acetilpiperazin-1-il)butoxi, 2-(4-isobutirilpiperazin-1-il)etoxi, 3-(4-isobutirilpiperazin-1-il)propoxi, 4-(4-isobutirilpiperazin-1-il)butoxi, 2-[4-(2-fluoroetil)piperazin-1-il]etoxi, 3-[4-(2-fluoroetil)piperazin-1-il]propoxi, 2-[4-(2,2,2-trifluoroetil)piperazin-1-il]etoxi, 3-[4-(2,2,2-trifluoroetil)piperazin-1-il]propoxi, 2-(4-cianometilpiperazin-1-il)etoxi, 3-(4-cianometilpiperazin-1-il)propoxi, 2-[2-(4-metilpiperazin-1-il)etoxi]etoxi, 2-cloroetoxi, 3-cloropropoxi, 4-clorobutoxi, 2-metilsulfoniletoxi, 3-metilsulfonilpropoxi, 2-(2-metoxietoxi)etoxi, 2-(4-piridiloxi)etoxi, 3-piridilmetoxi y 2-cianopirid-4-ilmetoxi;

n es 0 ó n es 1 y el grupo R^3 se localiza en la posición 5 ó 6 del grupo 2,3-metilendioxipiridin-4-ilo y se selecciona de cloro, bromo, trifluorometilo, ciano, hidroxi, metilo, etilo, metoxi y etoxi; o su sal de adición de ácido farmacéuticamente aceptable.

Un compuesto particular adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

Z es NH;

m es 1 y el grupo R^1 se localiza en la posición 5 y se selecciona de propoxi, isopropoxi, tetrahidropiran-4-iloxi, 4-piperidiniloxi y N-metilpiperidin-4-iloxi,

o m es 2 y el primer grupo R^1 se localiza en la posición 5 y se selecciona del grupo de sustituyentes listado inmediatamente arriba, y el segundo grupo R^1 se localiza en la posición 7 y se selecciona de 2-

pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]etoxi, 3-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]propoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 4-piperazin-1-ilbutoxi, 2-(4-metilpiperazin-1-il)etoxi, 3-(4-metilpiperazin-1-il)propoxi, 2-(4-alilpiperazin-1-il)etoxi, 3-(4-alilpiperazin-1-il)propoxi, 2-(4-prop-2-inilpiperazin-1-il)etoxi, 3-(4-prop-2-inilpiperazin-1-il)propoxi, 2-(4-acetilpiperazin-1-il)etoxi, 3-(4-acetilpiperazin-1-il)propoxi, 2-(4-isobutirilpiperazin-1-il)etoxi, 3-(4-isobutirilpiperazin-1-il)propoxi, 2-[4-(2,2,2-trifluoroetil)piperazin-1-il]etoxi y 3-[4-(2,2,2-trifluoroetil)piperazin-1-il]propoxi; y

n es 0 ó n es 1 y el grupo R^3 se localiza en la posición 5 ó 6 del grupo 2,3-metilendioxipiridin-4-ilo y se selecciona de fluoro, cloro, bromo, trifluorometilo y ciano; o su sal de adición de ácido farmacéuticamente aceptable.

Un compuesto particular adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

Z es NH;

m es 2 y el primer grupo R^1 se localiza en la posición 5 y se selecciona de isopropoxi y tetrahidropiran-4-iloxi, y el segundo grupo R^1 se localiza en la posición 7 y se selecciona de 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]etoxi, 3-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]propoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-(4-metilpiperazin-1-il)etoxi, 3-(4-metilpiperazin-1-il)propoxi, 2-(4-alilpiperazin-1-il)etoxi, 3-(4-alilpiperazin-1-il)propoxi, 2-(4-prop-2-inilpiperazin-1-il)etoxi, 3-(4-prop-2-inilpiperazin-1-il)propoxi, 2-(4-acetilpiperazin-1-il)etoxi, 3-(4-acetilpiperazin-1-il)propoxi, 2-(4-isobutirilpiperazin-1-il)etoxi, 3-(4-isobutirilpiperazin-1-il)propoxi, 2-[4-(2-hidroxietil)piperazin-1-il]etoxi, 3-[4-(2-hidroxietil)piperazin-1-il]propoxi, 2-[4-(2,2,2-trifluoroetil)piperazin-1-

il]etoxi, 3-[4-(2,2,2-trifluoroetil)piperazin-1-il]propoxi, 2-[4-(2-dimetilaminoacetil)piperazin-1-il]etoxi y 3-[4-(2-dimetilaminoacetil)piperazin-1-il]propoxi; y

n es 1 y el grupo R^3 se localiza en la posición 5 del grupo 2,3-metilendioxipiridin-4-ilo y se selecciona de cloro y bromo;

o su sal de adición de ácido farmacéuticamente aceptable.

Un compuesto particular adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

Z es NH;

m es 2 y el primer grupo R^1 se localiza en la posición 5 y se selecciona de isopropoxi y tetrahidropiran-4-iloxi, y el segundo grupo R^1 se localiza en la posición 7 y se selecciona de 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]etoxi, 3-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]propoxi,2-morfolinoetoxi, 3-morfolinopropoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-(4-metilpiperazin-1-il)etoxi, 3-(4-metilpiperazin-1-il)propoxi, 2-(4-alilpiperazin-1-il)etoxi, 3-(4-alilpiperazin-1-il)propoxi, 2-(4-prop-2-inilpiperazin-1-il)etoxi, 3-(4-prop-2-inilpiperazin-1-il)propoxi, 2-(4-acetilpiperazin-1-il)etoxi, 3-(4-acetilpiperazin-1-il)propoxi, 2-(4-isobutirilpiperazin-1-il)etoxi, 3-(4-isobutirilpiperazin-1-il)propoxi, 2-[4-(2,2,2-trifluoroetil)piperazin-1-il]etoxi y 3-[4-(2,2,2-trifluoroetil)piperazin-1-il]propoxi; y

n es 1 y el grupo R^3 se localiza en la posición 5 del grupo 2,3-metilendioxipiridin-4-ilo y se selecciona de cloro y bromo;

o su sal de adición de ácido farmacéuticamente aceptable.

Un compuesto particular adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

Z es NH;

m es 2 y el primer grupo R^1 se localiza en la posición 5 y se selecciona de isopropoxi y tetrahidropiran-4-iloxi, y el segundo grupo R^1 se localiza en la posición 7 y se selecciona de 2-pirrolidin-1-iletoxi, 2-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]etoxi, 2-morfolinoetoxi, 3-

morfolinopropoxi, 2-piperidinoetoxi, 2-piperazin-1-iletoxi, 2-(4-metilpiperazin-1-il)etoxi, 2-(4-prop-2-inilpiperazin-1-il)etoxi, 3-(4-prop-2-inilpiperazin-1-il)propoxi, 2-(4-acetilpiperazin-1-il)etoxi, 2-[4-(2-hidroxietil)piperazin-1-il]etoxi y 2-[4-(2-dimetilaminoacetil)piperazin-1-il]etoxi; y

n es 1 y el grupo R^3 se localiza en la posición 5 del grupo 2,3-metilendioxipiridin-4-ilo y es un grupo cloro;

o su sal de adición de ácido farmacéuticamente aceptable.

Un compuesto particular adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

Z es NH;

m es 2 y el primer grupo R^1 se localiza en la posición 5 y se selecciona de isopropoxi y tetrahidropiran-4-iloxi, y el segundo grupo R^1 se localiza en la posición 7 y se selecciona de 2-pirrolidin-1-iletoxi, 2-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]etoxi, 2-morfolinoetoxi, 2-piperidinoetoxi, 2-piperazin-1-iletoxi, 2-(4-metilpiperazin-1-il)etoxi, 2-(4-prop-2-inilpiperazin-1-il)etoxi,
2-(4-acetilpiperazin-1-il)etoxi) 2-[4-(2-hidroxietil)piperazin-1-il]etoxi y 2-[4-(2-dimetilaminoacetil)piperazin-1-il]etoxi; y

n es 1 y el grupo R^3 se localiza en la posición 5 del grupo 2,3-metilendioxipiridin-4-ilo y es un grupo cloro; o su sal de adición de ácido farmacéuticamente aceptable.

Un compuesto particular adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

Z es NH;

m es 2 y el primer grupo R^1 es un grupo 5-isopropoxi y el segundo grupo R^1 se localiza en la posición 7 y se selecciona de 2-pirrolidin-1-iletoxi, 2-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]etoxi, 2-morfolinoetoxi, 2-piperidinoetoxi, 2-piperazin-1-iletoxi, 2-(4-metilpiperazin-1-il)etoxi, 2-(4-acetilpiperazin-1-il)etoxi y 2-[4-(2-hidroxietil)piperazin-1-il]etoxi; y

n es 1 y el grupo R^3 se localiza en la posición 5 del grupo 2,3-

metilendioxipiridin-4-ilo y es un grupo cloro;
o su sal de adición de ácido farmacéuticamente aceptable.

Un compuesto particular adicional de la invención es un derivado de quinazolina de la Fórmula I en donde:

Z es NH;

m es 2 y el primer grupo R^1 es un grupo 5-isopropoxi y el segundo grupo R^1 se localiza en la posición 7 y se selecciona de 2-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]etoxi, 2-piperazin-1-iletoxi, 2-(4-metilpiperazin-1-il)etoxi, 2-(4-acetilpiperazin-1-il)etoxi y 2-[4-(2-hidroxietil)piperazin-1-il]etoxi; y

n es 1 y el grupo R^3 se localiza en la posición 5 del grupo 2,3-metilendioxipiridin-4-ilo y es un grupo cloro;
o su sal de adición de ácido farmacéuticamente aceptable.

Compuestos particulares de la invención son, por ejemplo, los derivados de quinazolina de la Fórmula I que se divulgan en el Ejemplo 3, y Ejemplo 6(1) a 6(7) más adelante.

Un compuesto particular de la invención es, por ejemplo, un derivado de quinazolina de la Fórmula I seleccionado de:-
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-metoxi-7-[3-(4-prop-2-inilpiperazin-1-il)propoxi]quinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-[3-(4-isobutirilpiperazin-1-il)propoxi]-6-metoxiquinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-metoxi-7-{3-[4-(2,2,2-trifluoroetil)piperazin-1-il]propoxi}quinazolina y
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-metoxi-7-[2-(4-prop-2-inilpiperazin-1-il)etoxi]quinazolina;
o su sal de adición de ácido farmacéuticamente aceptable.

Un compuesto particular adicional de la invención es, por ejemplo, un derivado de quinazolina de la Fórmula I seleccionado de:-
7-[2-(4-acetilpiperazin-1-il)etoxi]-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-tetrahidropiran-4-iloxiquinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-{2-[(3RS,4SR)-3,4-

118

metilendioxipirrolidin-1-il]etoxi}-5-tetrahidropiran-4-iloxiquinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-[2-(4-prop-2-inilpiperazin-1-il)etoxi]-5-tetrahidropiran-4-iloxiquinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-[3-(4-prop-2-inilpiperazin-1-il)propoxi]-5-tetrahidropiran-4-iloxiquinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(2-morfolinoetoxi)-5-tetrahidropiran-4-iloxiquinazolina y
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(3-morfolinopropoxi)-5-tetrahidropiran-4-iloxiquinazolina;
o su sal de adición de ácido farmacéuticamente aceptable.

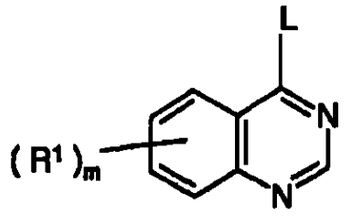
Un compuesto particular adicional de la invención es, por ejemplo, un derivado de quinazolina de la Fórmula I seleccionado de:-
7-[2-(4-acetilpiperazin-1-il)etoxi]-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxiquinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxi-7-(2-piperazin-1-iletoxi)quinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-{2-[4-(2-hidroxietil) piperazin-1-il]etoxi}-5-isopropoxiquinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxi-7-(2-pirrolidin-1-iletoxi)quinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxi-7-(2-piperidinoetoxi)quinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxi-7-(2-morfolinoetoxi)quinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxi-7-(3-morfolinopropoxi)quinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxi-7-[2-(4-prop-2-inilpiperazin-1-il)etoxi]quinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxi-7-[2-(4-metilpiperazin-1-il)etoxi]quinazolina y
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-{2-[4-(2-dimetilaminoacetil)piperazin-1-il]etoxi}-5-isopropoxiquinazolina;

119

o su sal de adición de ácido farmacéuticamente aceptable.

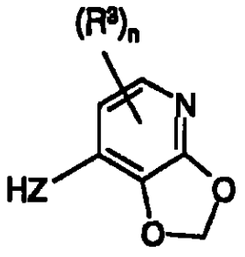
Un derivado de quinazolina de la Fórmula I, o su sal farmacéuticamente aceptable, puede prepararse por cualquier proceso conocido por ser aplicable a la preparación de compuestos químicamente relacionados. Tales procesos, cuando se usan para preparar un derivado de quinazolina de la Fórmula I se proporcionan como una característica adicional de la invención y se ilustran por los siguientes variantes de procesos representativos en los cuales, a menos que se especifique lo contrario, m, R^1, Z, n y R^3 tienen cualquiera de los significados definidos anteriormente. Materiales de partida necesarios pueden obtenerse por procedimientos estándar de química orgánica. La preparación de tales materiales de partida se describe en conjunción con las siguientes variantes de procesos representativos y dentro de los Ejemplos acompañantes. Materiales alternativamente necesarios pueden obtenerse por procedimientos análogos a los ilustrados, los cuales se encuentran dentro de las habilidades ordinarias de un profesional de la química orgánica.

(a) Para la producción de aquellos compuestos de la Fórmula I en donde Z es un grupo O, S o $N(R^2)$, la reacción de una quinazolina de la Fórmula II



II

en donde L es un grupo desplazable y m y R^1 tienen cualquiera de los significados definidos anteriormente, excepto que cualquier grupo funcional se protege, si es necesario, con un compuesto de la Fórmula III



III

en donde Z es O, S, o $N(R^2)$ y n, R^3 y R^2 tienen cualquiera de los

significados definidos anteriormente, excepto que cualquier grupo funcional se protege, si es necesario, tras lo cual cualquier grupo protector que esté presente se retira por medios convencionales.

La reacción puede llevarse convenientemente a cabo en la presencia de un ácido apropiado o en la presencia de una base adecuada. Un ácido apropiado es, por ejemplo, un ácido inorgánico tales como, por ejemplo, cloruro de hidrógeno o bromuro de hidrógeno. Una base adecuada es, por ejemplo, una base amina orgánica tal como, por ejemplo, piridina, 2,6-lutidina, colidina, 4-dimetilaminopiridina, trietilamina, morfolina, N-metilmorfolina o diazabiciclo[5.4.0]undec-7-eno, o, por ejemplo, un carbonato o hidróxido de metal alcalino o alcalinotérreo, por ejemplo carbonato de sodio, carbonato de potasio, carbonato de calcio, hidróxido de sodio o hidróxido de potasio, o, por ejemplo, una amida de metal alcalino, por ejemplo hexametildisilazano de sodio, o, por ejemplo, un hidruro de metal alcalino, por ejemplo hidruro de sodio.

Un grupo desplazable L apropiado es, por ejemplo, un grupo halógeno alcoxi, ariloxi o sulfoniloxi, por ejemplo un grupo cloro, bromo, metoxi, fenoxi, pentafluorofenoxi, metansulfoniloxi o toluen-4-sulfoniloxi. La reacción se lleva convenientemente a cabo en la presencia de un disolvente inerte apropiado o diluyente, por ejemplo un alcohol o éster tal como metanol, etanol, isopropanol o acetato de etilo, un disolvente halogenado tal como cloruro de metileno, cloroformo o tetracloruro de carbono, un éter tal como tetrahidrofurano ó 1,4-dioxano, un disolvente aromático tal como tolueno, o un disolvente aprótico dipolar tal como N,N-dimetilformamida, N,N-dimetilacetamida, N-metilpirrolidin-2-ona de sulfóxido dimetílico. La reacción puede llevarse convenientemente a cabo a una temperatura en el rango, por ejemplo, 0 a 250°C, preferiblemente en el rango 0 a 120°C.

Típicamente, la quinazolina de la Fórmula II puede hacerse reaccionar con un compuesto de la Fórmula III en la presencia de un disolvente aprótico tal como N,N-dimetilformamida, convenientemente en la presencia de una base, por ejemplo carbonato de potasio o

hexametildisilazano de sodio, y a una temperatura en el rango, por ejemplo, 0 a 150°C, preferiblemente en el rango, por ejemplo, 0 a 70°C.

El derivado de quinazolina de la Fórmula I puede obtenerse de este proceso en la forma de la base libre o alternativamente puede obtenerse en la forma de una sal con el ácido de la Fórmula H-L en donde L tiene el significado definido anteriormente. Cuando se desea obtener la base libre de la sal, la sal puede tratarse con una base apropiada, por ejemplo, una base amina orgánica tal como, por ejemplo, piridina, 2,6-lutidina, colidina, 4-dimetilaminopiridina, trietilamina, morfolina, N-metilmorfolina o diazabiciclo[5.4.0]undec-7-eno, o, por ejemplo, un carbonato o hidróxido de metal alcalino o alcalinotérreo, por ejemplo carbonato de sodio, carbonato de potasio, carbonato de calcio, hidróxido de sodio o hidróxido de potasio.

Los grupos protectores pueden seleccionarse en general de cualquiera de los grupos descritos en la literatura o conocidos por el químico experto como apropiados para la protección del grupo en cuestión y pueden introducirse por métodos convencionales. Los grupos protectores pueden retirarse por cualquier método conveniente como se describe en la literatura o por el químico experto como apropiados para la extracción del grupo protector en cuestión, escogiéndose tales métodos de modo que efectúen la extracción del grupo protector con el mínimo de alteración de los grupos en cualquier otra parte de la molécula.

A continuación se dan ejemplos específicos de grupos protectores por razones de conveniencia, en los cuales "inferior", como en, por ejemplo, alquilo inferior, significa que el grupo al cual se aplica tiene preferiblemente 1-4 átomos de carbono. Se entenderá que estos ejemplos no son exhaustivos. Donde más adelante se den ejemplos específicos de métodos para la extracción de grupos protectores, éstos, análogamente no son exhaustivos. Naturalmente, el uso de grupos protectores y métodos de desprotección no mencionados en forma específica se encuentra dentro del ámbito de la invención.

Un grupo protector carboxi puede ser el residuo de un alcohol

122

alifático o arilalifático formador de un éster o de un silanol formador de un éster (conteniendo dicho alcohol o silanol preferiblemente 1-20 átomos de carbono). Ejemplos de grupos protectores carboxi incluyen grupos (1-12C)alquilo de cadena recta o ramificada (por ejemplo isopropilo, y tert-butilo); grupos alquilo inferior-alcoxi inferior (por ejemplo metoximetilo, etoximetilo e isobutoximetilo); grupos alquilo inferior-aciloxi inferior, (por ejemplo acetoximetilo, propioniloximetilo, butiriloximetilo y pivaloiloximetilo); grupos alquilo inferior-alcoxicarboniloxi inferior (por ejemplo 1-metoxicarboniloxietilo y 1-etoxicarboniloxietilo); grupos alquilo inferior-arilo (por ejemplo bencilo, 4-metoxibencilo, 2-nitrobencilo, 4-nitrobencilo, benzhidrilo y ftalidilo); grupos tri(alquilo inferior)sililo (por ejemplo trimetilsililo y tert-butildimetilsililo); grupos alquilo inferior-tri(alquilo inferior)sililo (por ejemplo trimetilsililetilo); y grupos (2-6C)alquenilo (por ejemplo alilo). Métodos particularmente apropiados para la extracción de los grupos protectores carboxilo incluyen por ejemplo escisión catalizada por ácido, base, metal ó enzima.

Ejemplos de grupos protectores hidroxi incluyen grupos alquilo inferior (por ejemplo tert-butilo), grupos alquenilo inferior (por ejemplo alilo); grupos alcanoilo inferior (por ejemplo acetilo); grupos alcoxicarbonilo inferior (por ejemplo tert-butoxicarbonilo); grupos alqueniloxicarbonilo inferior (por ejemplo aliloxicarbonilo); grupos alcoxicarbonilo inferior-arilo (por ejemplo benciloxicarbonilo, 4-metoxibenciloxicarbonilo, 2-nitrobenciloxicarbonilo y 4-nitrobenciloxicarbonilo); grupos tri(alquilo inferior)sililo (por ejemplo trimetilsililo y tert-butildimetilsililo) y grupos alquilo inferior-arilo (por ejemplo bencilo).

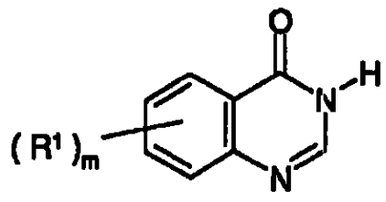
Ejemplos de grupos protectores amino incluyen formilo, grupos alquilo inferior-arilo (por ejemplo bencilo y bencilo sustituido, 4-metoxibencilo, 2-nitrobencilo y 2,4-dimetoxibencilo, y trifenilmetilo); grupos di-4-anisilmetilo y furilmetilo; grupos alcoxicarbonilo inferior (por ejemplo tert-butoxicarbonilo): grupos alqueniloxicarbonilo inferior (por ejemplo aliloxicarbonilo); grupos alcoxicarbonilo inferior-arilo (por

ejemplo benciloxicarbonilo, 4-metoxibenciloxicarbonilo, 2-nitrobenciloxicarbonilo y 4-nitrobenciloxicarbonilo); grupos trialquilsililo (por ejemplo trimetilsililo y tert-butildimetilsililo); grupos alquilideno (por ejemplo metilideno) y grupos bencilideno y bencilideno sustituido.

Métodos apropiados para la extracción de grupos protectores hidroxi y amino incluyen, por ejemplo, hidrólisis catalizada por ácido, base, metal ó enzimas para grupos tales como 2-nitrobenciloxicarbonilo, hidrogenación para grupos tales como bencilo y fotolíticamente para grupos tales como 2-nitrobenciloxicarbonilo.

Se remite al lector a Advanced Organic Chemistry, 4th Edition, by J. March, publicada por John Wiley & Sons 1992, para guía general sobre las condiciones de reacción y reactivos; y a Protective Groups in Organic Synthesis, 2nd Edition, by T. Green *et al.*, también publicada por John Wiley & Son, para guía general sobre grupos protectores.

Los materiales de partida de quinazolina de la Fórmula II pueden obtenerse por procedimientos convencionales tales como los divulgados en las Solicitudes Internacionales de Patente WO 01/94341 y WO 02/16352. Por ejemplo, una 1,4-dihidroquinolin-4-ona de Fórmula IV



IV

en donde m y R^1 tienen cualquiera de los significados definidos anteriormente excepto que cualquier grupo funcional se protege, si es necesario, puede hacerse reaccionar con un agente halogenante tal como cloruro de tionilo, cloruro de fosforilo o una mezcla de tetracloruro de carbono y trifenilfosfamida, tras lo cual cualquier grupo protector, que esté presente, se retira por medios convencionales.

La 4-cloroquinazolina así obtenida puede convertirse, si se requiere, en una 4-pentafluorofenoxiquinazolina mediante la reacción con pentafluorofenol en la presencia de una base adecuada tal como carbonato

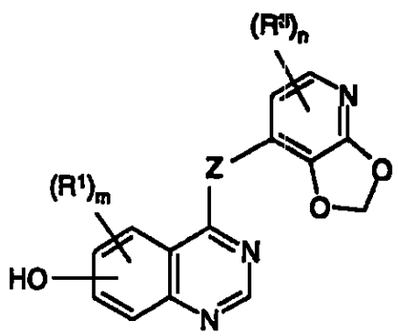
de potasio y en la presencia de un disolvente apropiado tal como N,N-dimetilformamida.

Los materiales de partida de la 4-amino-2,3-metilendioxipiridina (Fórmula III, por ejemplo cuando Z es NH) pueden obtenerse por procedimientos convencionales como se ilustra en los Ejemplos. Los materiales correspondientes de la 4-hidroxi- y 4-mercapto-2,3-metilendioxipiridina (Fórmula III, cuando Z es O o S respectivamente) pueden obtenerse por procedimientos convencionales,

(b) Para la producción de aquellos compuestos de la Fórmula I en donde por lo menos un grupo R^1 es un grupo de la fórmula

$$Q^1 - X^1-$$

en donde Q^1 es un grupo aril-(1-6C)alquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo:(1-6C)alquilo o heterociclil-(1-6C)alquilo o un grupo alquilo opcionalmente sustituido y X^1 es un átomo de oxígeno, el acoplamiento, convenientemente en la presencia de un agente deshidratante apropiado, de una quinazolina de la Fórmula V



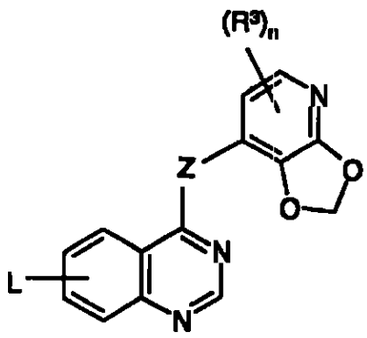
V

en donde m, R^1, Z, n y R^3 tienen cualquiera de los significados definidos anteriormente, excepto que cualquier grupo funcional se protege, si es necesario, con un alcohol apropiado, tras lo cual cualquier grupo protector, que esté presente, se retira por medios convencionales.

Un agente deshidratante adecuado es, por ejemplo, un reactivo de carbodiimida tal como diciclohexilcarbodiimida o 1-(3-dimetilaminopropil)-3-etilcarbodiimida o una mezcla de un compuesto azo tal como dietil o di-tert-butil azodicarboxilato y una fosfamida tal como trifenilfosfamida. La reacción se lleva convenientemente a cabo en la

presencia de un disolvente o diluyente inerte apropiado, por ejemplo un disolvente halogenado tal como cloruro de metileno, cloroformo o tetracloruro de carbono y a una temperatura en el rango, por ejemplo, 10 a 150°C, preferiblemente a temperatura ambiente o cerca de ella.

(c) Para la producción de aquellos compuestos de la Fórmula I en donde un grupo R^1 contiene un grupo (1-6C)alcoxi o (1-6C)alcoxi sustituido o un grupo (1-6C)alquilamino o (1-6C)alquilamino sustituido, la reacción, convenientemente en la presencia de una base apropiada, como se define anteriormente, de un derivado de quinazolina de la Fórmula VI



VI

en donde L es un grupo desplazable como se define anteriormente y Z, n y R^3 tienen cualquiera de los significados definidos anteriormente, excepto que cualquier grupo funcional se protege, si es necesario, con un alcohol o amina, según lo apropiado, tras lo cual cualquier grupo protector, que esté presente, se retira por medios convencionales.

La reacción se lleva convenientemente a cabo en la presencia de un diluyente o vehículo inerte adecuado como se define anteriormente y a una temperatura en el rango 10 a 150°C, preferiblemente a 50°C o cerca a esta temperatura.

(d) Para la producción de aquellos compuestos de la Fórmula I en donde R^1 es un grupo (1-6C)alcoxi amino-sustituido (tal como un grupo 2-(4-metilpiperazin-1-il)etoxi ó 3-dimetilaminopropoxi), la reacción de un compuesto de la Fórmula I en donde R^1 es un grupo (1-6C)alcoxi halógeno-sustituido con un compuesto heterociclilo que contiene nitrógeno o una amina apropiada.

La reacción se lleva convenientemente a cabo en la presencia de un diluyente o vehículo inerte apropiado como se define anteriormente y a una temperatura en el rango 10 a 180°C, preferiblemente en el rango 60 a 120°C.

(e) Para la producción de aquellos compuestos de la Fórmula I en donde R^1 es un grupo (1-6C)alcoxi amino-hidroxi-disustituido (tal como 2-hidroxi-3-pirrolidin-1-ilpropoxi ó 3-[N-alil-N-metilamino]-2-hidroxipropoxi), la reacción de un compuesto de la Fórmula I en donde el grupo R^1 contiene un grupo (1-6C)alcoxi epoxi-sustituido con un compuesto heterociclilo o una amina apropiada.

La reacción se lleva convenientemente a cabo en la presencia de un diluyente o vehículo inerte apropiado como se define anteriormente y a una temperatura en el rango 10 a 150°C, preferiblemente a temperatura ambiente o cerca de ella.

(f) Para la producción de aquellos compuestos de la Fórmula I en donde Z es un grupo SO ó SO_2, la oxidación de un compuesto de Fórmula I en donde Z es un grupo S.

Los reactivos de oxidación convencionales y las condiciones de reacción para tal oxidación parcial o completa de un átomo de azufre son bien conocidos por el profesional en química orgánica.

(g) Para la producción de aquellos compuestos de la Fórmula I en donde un grupo R^1 contiene un grupo heterocíclico N-acilado, la acilación, convenientemente en la presencia de una base apropiada, como se define anteriormente, de un derivado de quinazolina de la Fórmula I en donde el grupo R^1 contiene un grupo heterocíclico con un grupo NH no sustituido.

Agentes acilantes adecuados son bien conocidos por la persona experta en el arte y sus ejemplos se ilustran en los Ejemplos. Por ejemplo, un compuesto de la Fórmula I en donde un grupo R^1 contiene un grupo piperidinilo piperazinilo con un grupo NH no sustituido puede hacerse reaccionar bajo condiciones convencionales con un ácido carboxílico sustituido de manera opcional o su derivado reactivo.

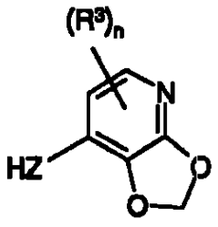
Un derivado reactivo apropiado de un ácido carboxílico sustituido de

manera opcional es, por ejemplo, un haluro de ácido carboxílico; una amida de ácido carboxílico; un anhídrido mixto, por ejemplo un anhídrido formado por la reacción del ácido carboxílico y un cloroformiato tal como isobutil cloroformiato; el producto de la reacción del ácido carboxílico con una carbodiimida tal como diciclohexilcarbodiimida o 1-(3-dimetilaminopropil)-3-etilcarbodiimida; el producto de la reacción del ácido carboxílico con una mezcla de un compuesto azo tal como dietil o di-*tert*-butil azodicarboxilato y una fosfamida tal como trifenilfosfamida; o el producto de la reacción del ácido carboxílico con una sal de uronio tal como hexafluorofosfato de (V)2-(7-azabenzotriazol-1-il)-1,1,3,3-tetrametiluronio. Por ejemplo, un ácido carboxilico amino-sustituido apropiado es N,N-dimetilglicina y su derivado reactivo adecuado es cloruro de 2-dimetilaminoacetilo.

La reacción se lleva convenientemente a cabo en la presencia de un diluyente o vehículo inerte apropiado, como se define anteriormente, y a una temperatura en el rango 10 a 150°C, preferiblemente a temperatura ambiente o cerca de ella.

Cuando se requiere una sal farmacéuticamente aceptable de un derivado de quinazolina de la Fórmula I, por ejemplo, una sal de adición de ácido, ésta puede obtenerse, por ejemplo, por la reacción de dicho derivado de quinazolina con un ácido apropiado usando un procedimiento convencional.

Muchos de los intermedios definidos aquí son novedosos y éstos se proveen como una característica adicional de la invención. Por ejemplo, muchos compuestos de la Fórmula III



III

en donde Z es O, S, ó N(R^2) y n, R^3 y R^2 tienen cualquiera de los

128

significados definidos anteriormente son compuestos novedosos. Por ejemplo, aunque los materiales de partida de la 4-amino-2,3-metilendioxipiridina (Fórmula III, por ejemplo cuando Z es NH) pueden obtenerse por procedimientos convencionales como se ilustra en los Ejemplos; compuestos tales como 4-amino-5-cloro-2,3-metilendioxipiridina es un compuesto novedoso que se provee como una característica adicional de la invención.

Análisis Biológicos

Los siguientes análisis pueden usarse para medir los efectos de los compuestos de la presente invención como inhibidores de tirosina cinasa c-Src, como inhibidores in vitro de la proliferación de células de fibroblastos transinfectadas con c-Src, como inhibidores in vitro de la migración de las células neoplásicas del pulmón humanas A549, como inhibidores in vivo del crecimiento en ratones sin pelaje de xenoinjertos de tejido A549, y para la inhibición in vitro del canal de potasio codificado por hERG,

(a) Análisis Enzimático In Vitro

Usando un análisis Elisa convencional se evaluó la capacidad de los compuestos de prueba para inhibir la fosforilación de un sustrato polipéptido, que contenía tirosina, por la enzima c-Src cinasa.

Una solución de sustrato [100µl de una solución de 20µg/ml del ácido poliamino Poly(Glu, Tyr) 4:1 (Catálogo Sigma No. P0275) en solución salina tamponada con fosfato (PBS) que contenía 0.2mg/ml de azida de sodio] se agregó a cada pozo de un número de inmunoplacas de 96 pozos Nunc (Catálogo No. 439454) y las placas se sellaron y se almacenaron a 4°C durante 16 horas. Se descartó el exceso de solución de sustrato, y alícuotas de Seroalbúmina Bovina (BSA; 150µl de una solución al 5% en) se transfirieron a cada pozo de análisis recubierto con sustrato y se incubaron durante 1 hora a temperatura ambiente para bloquear la unión no específica. Los posos de las placas de análisis se lavaron alternativamente con PBS que contenía 0.05% v/v Tween 20 (PBST) y con solución amortiguadora Hepes pH7.4 (50mM, 300µl/pozo) antes de someterse a inmunotransferencia en seco.

Cada compuesto de prueba se disolvió en sulfóxido de dimetilo y se diluyó con agua destilada para producir una serie de diluciones (de 100µM a 0.001µM). Porciones (25µl) de cada dilución del compuesto de prueba se transfirieron a pozos en las placas de análisis lavadas. Pozos de control "total" contenína DMSO diluido en lugar de compuesto. Alícuotas (25µl) de una solución de cloruro de magnesio acuoso (80mM) que contenía adenosina-5' trifosfato (ATP; 40µM) se agregó a todos los pozos de prueba, excepto los pozos de control "blanco" que contenían cloruro de magnesio sin ATP.

c-Src cinasa humana activa (enzima recombinante expresada en células de insecto Sf9; obtenidas de Upstate Biotechnology Inc., producto 14-117) se diluyó inmediatamente antes del uso por un factor de 1:10.000 con un diluyente enzimático que comprendía 100mM de solución amortiguadora (***"buffer"***) Hepes pH7.4, 0.2mM ortovanadato de sodio, 2mM ditiotreitol y 0.02% BSA. Para iniciar las reacciones, se agregaron alícuotas (50µl) de enzima diluida fresca a cada pozo y las placas se incubaron a temperatura ambiente durante 20 minutos. El líquido sobrenadante en cada pozo se descartó y los pozos se lavaron dos veces con PBST. Anticuerpo anti-fosfotirosina IgG de ratón (Upstate Biotechnology Inc., producto 05-321; 100µl) se diluyó por un factor de 1:6000 con PBST que contenía 0.5% p/v BSA y se agregó a cada pozo. Las placas se incubaron durante 1 hora a temperatura ambiente. El líquido sobrenadante se descartó y cada pozo se lavó con PBST (x4). Anticuerpo Ig anti-ratón de oveja enlazado a peroxidasa de rábano (HRP) (Catálogo Amersham No. NXA 931; 100µl) se diluyó por un factor de 1:500 con PBST que contenía 0.5% p/v BSA y se agregó a cada pozo. Las placas se incubaron durante 1 hora a temperatura ambiente. El líquido sobrenadante se descartó y los pozos se lavaron con PBST (x4).

Una cápsula PCSB (Catálogo Sigma No. P4922) se disolvió en agua destilada (100ml) para promover una solución amortiguadora fosfato-citrato pH5 (50mM) que contenía 0.03% de perborato de sodio. Una alícuota (50ml) de esta solución amortiguadora se mezcló con una tableta de 50mg

de 2,2'-azinobis(ácido 3-etilbenzotiazolin-6-sulfónico) (ABTS; Catálogo Boehringer No. 1204 521). Alícuotas (100µl) de la solución resultante se agregaron a cada pozo. Las placas se incubaron durante 20 a 60 minutos a temperatura ambiente hasta que el valor de la densidad óptica de los pozos de control "total", medido a 405nm usando un espectrómetro de lectura de placas, fue de aproximadamente1.0. Se utilizaron valores de control "blanco" (sin ATP) y "total" (sin compuesto) para determinar el rango de dilución del compuesto de prueba, que produjeron 50% de inhibición de la actividad enzimática,

(b) Análisis de Proliferación de Fibroblastos NIH 3T3 (c-src 3T3) transinfectados con c-Src In Vitro

Este análisis determinó la capacidad de un compuesto de prueba para inhibir la proliferación de células de fibroblastos 3T3 de ratón del instituto Nacional de Salud (NIH), que habían sido transinfectados establemente con un mutante activador (Y530F) de c-Src humana.

Usando un procedimiento similar al descrito por Shalloway *et al.*, Cell, 1987, 49, 65-73, se transinfectaron células NIH 3T3 con un mutante activador (Y530F) de c-Src humana. Las células c-Src 3T3 resultantes se sembraron típicamente a 1.5 x 10^4 células por pozo en placas de análisis transparentes de 96 pozos, tratadas con cultivo de tejido (Costar), que contenína cada una un medio de análisis que comprendía Dulbecco's modified Eagle's medium (DMEM; Sigma) más 0.5% suero fetal bovino (FCS), 2mM glutamina, 100 unidades/ml de penicilina y 0.1mg/ml de estreptomicina en 0.9% solución de cloruro de sodio acuoso. Las placas se incubaron de un día para otro a 37°C en un incubador humidificado (7.5% CO_2: 95% aire).

Compuestos de prueba se solubilizaron en DMSO para formar una solución madre 10mM. Alícuotas de la solución madre se diluyeron con el medio DMEM descrito más arriba y se agregaron a pozos apropiados. Se hicieron diluciones en serie para producir un rango de concentraciones de prueba. En cada placa se incluyeron pozos de control a los cuales no se agregó compuesto de prueba. Las placas se incubaron de un día para otro a

37°C en un incubador humidificado (7.5% CO_2: 95% aire).

Reactivo marcador BrdU (Catálogo Boehringer Mannheim No. 647 229) se diluyó por un factor de 1:100 en medio DMEM que contenía 075% FCS y se agregaron alícuotas (20µl) a cada pozo para producir una concentración final de 10µM). Las placas se incubaron a 37°C durante 2 horas. El medio se decantó. Una solución desnaturalizante (solución FixDenat, Catálogo Boehringer Mannheim No. 647 229; 50µl) se agregó a cada pozo y las placas se pusieron en un agitador de placas a temperatura ambiente durante 45 minutos. El sobrenadante se decantó y los pozos se lavaron con PBS (200µl por pozo). Solución de anti-BrdU-peroxidasa (Catálogo Boehringer Mannheim No. 647 229) se diluyó por un factor de 1:100 en PBS que contenía 1% BSA y 0.025% leche en polvo descremada (Marvel (marca comercial registrada), Premier Beverages, Stafford, GB) y se agregó una alícuota (100µl) de la solución resultante a cada pozo. Las placas se pusieron sobre un agitador de placas a temperatura ambiente durante 90 minutos. Los pozos se lavaron con PBS (x5) para garantizar la eliminación de un conjugado de anticuerpo no ligado. Las placas se sometieron a inmunotransferencia en seco y se agregó a cada pozo solución de sustrato de tetrametilbenzidina (Catálogo Boehringer Mannheim No. 647 229; 100µl). Las placas se agitaron suavemente en un agitador de placas mientras se desarrollaba color durante un período de 10 a 20 minutos. La absorbencia de los pozos se midió a 690nm. Se determinó la magnitud de inhibición de la proliferación celular en un rango de concentraciones de cada compuesto de prueba y se derivó un valor IC_{50} anti-proliferativo,

(c) Análisis de Migración de Micro-Gotícula In Vitro

Este análisis determina la capacidad de un compuesto de prueba para inhibir la migración de estirpes de células adherentes de mamífero, por ejemplo la estirpe de células neoplásicas humanas A549.

Medio RPMI (Sigma) que contenía 10% FCS, 1% L-glutamina y 0.3% agarosa (Catálogo Difco No. 0142-01) se calentó a 37°C en un baño de agua. Una solución madre de agar acuoso al 2% se trató en una autoclave y se almacenó a 42°C. Se agregó una alícuota (1.5 ml) de la solución de agar

al medio RPMI (10 ml) inmediatamente antes de su uso. Células A549 (No. de Acceso ATCC CCL185) se suspendieron en una concentración de 2 x 10^7 células/ml en el medio y se mantuvieron a una temperatura de 37°C.

Una gotícula (2µl) de la mezcla célula/agarosa se transfirió mediante pipeta al centro de cada pozo de un número de placa de microvaloración tratada con cultivo de tejido, de fondo plano, de 96 pozos (Catálogo Bibby Sterilin No. 642000). Las placas se pusieron brevemente sobre hielo para acelerar la gelatinización de las gotículas que contenían agarosa. Alícuotas (90µl) de medio que se habían enfriado a 4°C se transfirieron a cada pozo, teniendo cuidado de no alterar las microgotículas. Compuestos de prueba se diluyeron de una solución madre 10mM en DMSO usando medio RPMI como se describe anteriormente. Alícuotas (10µl) de los compuestos de prueba diluidos se transfirieron a los pozos, poniendo cuidado nuevamente de no alterar las microgotículas. Las placas se incubaron a 37°C en un incubador humidificado (7.5% CO_2: 95% aire) durante alrededor de 48 horas.

Se evaluó la migración visualmente y se reevaluó la distancia de migración al borde de la gotícula de agar. Se derivó una IC_{50} inhibidora migratoria graficando la medida de migración media contra la concentración del compuesto de prueba.

(d) Análisis de Crecimiento de Xencinjerto A549 In Vivo

Esta prueba mide la capacidad de los compuestos de inhibir el crecimiento del carcinoma humano A549 desarrollado en ratones sin pelambre atímicos (cepa Alderley Park nu/nu). Un total de alrededor de 5 x 10^6 células A549 en matrigel (Catálogo Beckton Dickinson No. 40234) se inyectaron subcutáneamente en el costado izquierdo de cada ratón de prueba y los tumores resultantes se dejaron crecer durante alrededor de 14 días. Se midió el tamaño de los tumores dos veces por semana usando calibres y se calculó un volumen teórico. Los animales se seleccionaron para proporcionar grupos de tratamiento y control de volumen de tumores promedio aproximadamente iguales. Se prepararon compuestos de prueba como una suspensión molida en un molino de bolas en vehículo de

polisorbato al 1% y se administraron oralmente una vez al día durante un período de alrededor de 28 días. Se evaluó el efecto del crecimiento de los tumores.

(e) Prueba de Canal de Potasio codificado por hERG

Este análisis determina la capacidad de un compuesto de prueba de inhibir la corriente de cola que fluye a través del canal de potasio codificado por el hERG.

Células renales embrionarias humanas (HEK) que expresan el canal codificado por hERG se cultivaron en Minimum Essential Medium Eagle (EMEM; Sigma-Aldrich catálogo número M2279), suplementado con 10% Suero Fetal Bovino (Labtech International; producto número 4-101-500), 10% M1 suplemento libre de suero (Egg Technologies; producto número 70916) y 0.4 mg/ml Geneticin G418 (Sigma-Aldrich; catálogo número G7034). Uno o dos días antes de cada experimento, las células se desprendieron de los matraces de cultivo de tejido con Accutase (TCS Biologicals) usando métodos de cultivo de tejido estándar. Luego se pusieron sobre cubiertas de vidrio apoyadas en los pozos de una placa de 12 pozos y se cubrieron con 2 ml del medio de cultivo.

Para cada célula registrada, se puso una cubierta de vidrio que contenía las células en la base de una cámara Perspex que contenía solución de baño (ver más adelante) a temperatura ambiente (~20 °C). Esta cámara se fijó a la plataforma de un microscopio invertido de contraste de fase. Inmediatamente después de poner la cubierta de vidrio en la cámara, se irrigó solución de baño en la cámara desde un reservorio alimentado por gravedad durante 2 minutos con un caudal de ~ 2 ml/min. Transcurrido este tiempo, se detuvo la irrigación.

Una pipeta de conexión hecha de tubo de vidrio de borosilicato (GC120F, Harvard Apparatus) usando un generador de micropipeta P-97 (Sutter Instrument Co.) se llenó con solución para pipetas (ver más adelante). La pipeta estaba conectada a la placa de toma del amplificador de pinchamiento de membrana (Axopatch 200B, Axon Instruments) mediante un alambre de cloruro de plata/plata. La masa de la placa de toma

estaba conectada al electrodo a tierra. Ésta consistía de un alambre de cloruro de plata/plata empotrado en 3% de agar compuesto con 0.85% de cloruro de sodio.

La célula se registró en toda la configuración celular de la técnica de pinchamiento de membrana. Luego de la "poración" (***"break-in"***), la cual se hizo con un potencial de sostenimiento de -80 mV (fijado por el amplificador), y ajuste apropiado de resistencia en serie y controles de capacitancia, se utilizó software de electrofisiología (*Clampex,* Axon Instruments) para fijar un potencial de sostenimiento (-80 mV) y para proporcionar un protocolo de voltaje. Este protocolo se aplicó cada 15 segundos y constó de un paso de 1 s a +40 mV seguido por un paso de 1 s a -50 mV. La respuesta de corriente a cada protocolo de voltaje impuesto se filtró con pasabajos por el amplificador a 1 kHz. Se adquirió entonces la señal filtrada, en línea, digitalizando esta señal análoga del amplificador con un convertidor análogo a digital. La señal digitalizada se capturó luego en un computador que ejecutaba software *Clampex* (Axon Instruments). Durante el potencial de sostenimiento y el paso a + 40 mV la corriente se muestreó a 1 kHz. La tasa de muestreo se fijó seguidamente a 5 kHz para el resto del protocolo de voltaje.

Las composiciones, pH y osmolaridad del baño y la solución para las pipetas se tabulan a continuación.

Sal	Pipeta (mM)	Baño (mM)
NaCl	-	137
KCl	130	4
$MgCl_2$	1	1
$CaCl_2$	-	1.8
HEPES	10	10
Glucosa	-	10
Na_2ATP	5	-
EGTA	5	-

Parámetro	Pipeta	Baño
pH	7.18-7.22	7.40

Ajuste de pH con	1M KOH	1M NaOH
Osmolaridad (mOsm)	275-285	285-295

La amplitud de la corriente de cola del canal de potasio codificado por hERG luego del paso de +40 mV a -50 mV se registró en línea mediante software *Clampex* (Axon Instruments). Luego de la estabilización de la amplitud de la corriente de cola, se aplicó a la célula solución de baño que contenía el vehículo para la sustancia de prueba. Previendo que la aplicación de vehículo no tuviera un efecto significativo sobre la amplitud de la corriente de cola, se construyó entonces una curva de efecto de concentración acumulativa al compuesto.

El efecto de cada concentración del compuesto de prueba se cuantificó expresando la amplitud de la corriente de cola en la presencia de una concentración dada de compuesto de prueba como porcentaje de él, en la presencia de vehículo. La potencia del compuesto de prueba (IC_{50}) se determinó ajustando los valores de inhibición porcentual que conformaban el efecto de concentración a una ecuación Hill de cuatro parámetros usando un paquete estándar de ajuste de datos. Si el nivel de inhibición observado en la concentración máxima de prueba no excedía el 50%, no se producía valor de potencia y se citaba un valor de inhibición porcentual a esa concentración.

Las pruebas de isoenzima citocromo P450 pueden conducirse por medios convencionales.

Aunque las propiedades farmacológicas de los compuestos de la Fórmula I varían con el cambio estructural, de acuerdo con lo esperado, en general, la actividad poseida por los compuestos de la Fórmula I puede demostrarse con las siguientes concentraciones o dosis en una o más de las pruebas anteriores (a), (b), (c) y (d):-

Prueba (a):- IC_{50} en el rango, por ejemplo, 0.001 -10 µM;

Prueba (b):- IC_{50} en el rango, por ejemplo, 0.01 - 20 µM;

Prueba (c):- actividad en el rango, por ejemplo, 0.1-25 µM;

Prueba (d):- actividad en el rango, por ejemplo, 1-200 mg/kg/día.

En general, muchos de los compuestos particulares de la Fórmula I provistos más adelante como Ejemplos poseen actividad con las siguientes concentraciones o dosis en una o más de las pruebas anteriores (a), (b), (c) y (d):-

Prueba (a):- IC_{50} en el rango, por ejemplo, 0.001 - 0.1 μM;

Prueba (b):- IC_{50} en el rango, por ejemplo, 0.01 -1 μM;

Prueba (c):- actividad en el rango, por ejemplo, 0.1-1 μM;

Prueba (d):- actividad en el rango, por ejemplo, 1-200 mg/kg/día.

No se observó toxicidad fisiológicamente inaceptable en Prueba (d) con la dosis efectiva para compuestos analizados de la presente invención. En consecuencia, no se esperan efectos toxicológicos adversos cuando un compuesto de Fórmula I, o su sal farmacéuticamente aceptable, como se define anteriormente se administra en rangos de formulación definidos más adelante.

De acuerdo con aspecto adicional de la invención se provee una composición farmacéutica que comprende un derivado de quinazolina de la Fórmula I, o su sal farmacéuticamente aceptable, como se define anteriormente en asociación con un diluyente o vehículo farmacéuticamente aceptable.

Las composiciones de la invención pueden estar en una forma apropiada para uso oral (por ejemplo como tabletas, pastillas para chupar, cápsulas duras o blandas, suspensiones acuosas u oleosas, emulsiones, polvos o gránulos dispersables, jarabes o elíxires), para uso local (por ejemplo como cremas, ungüentos, geles, o soluciones o suspensiones acuosas u oleosas), para administración por inhalación (por ejemplo como un polvo finamente dividido o un aerosol líquido), para administración por insuflación (por ejemplo como un polvo finamente dividido) o para administración parenteral (por ejemplo como una solución acuosa u oleosa estéril para administración intravenosa, subcutánea, intramuscular o como supositorio para administración rectal).

Las composiciones de la invención pueden obtenerse por procedimientos convencionales usando excipientes farmacéuticos

convencionales, bien conocidos en el arte. Por consiguiente, las composiciones previstas para uso oral pueden contener, por ejemplo, uno o más agentes colorantes, edulcorantes, saborizantes y/o preservantes.

La cantidad de ingrediente activo que se combina con uno o más excipientes para producir una formulación farmacéutica única variará necesariamente dependiendo del anfitrión tratado y de la vía particular de administración. Por ejemplo, una formulación prevista para administración oral a humanos contendrá por lo general, por ejemplo, de 0.5 mg a 0.5 g de agente activo (más convenientemente de 0.5 a 100 mg, por ejemplo de 1 a 30 mg) compuesto con una cantidad apropiada y conveniente de excipientes que pueden variar de alrededor de 5 a alrededor de 98 por ciento en peso de la composición total.

El tamaño de la dosis con fines terapéuticos o profilácticos de un compuesto de la Fórmula I variará naturalmente de acuerdo con naturaleza y gravedad de las afecciones, la edad y el sexo del paciente o animal y de la vía de administración, de acuerdo con principios bien conocidos de medicina.

Cuando se emplea un compuesto de la Fórmula I con fines terapéuticos o profilácticos, se administrará generalmente de modo que se reciba una dosis diaria en el rango, por ejemplo, 0.1 mg/kg a 75 mg/kg de peso corporal, administrada, si se requiere, en dosis divididas. En general se administrarán dosis menores cuando se emplee una vía parenteral. Así, por ejemplo, para administración intravenosa, se usará generalmente una dosis en el rango, por ejemplo, 0.1 mg/kg a 30 mg/kg de peso corporal. Análogamente, para administración por inhalación, se empleará una dosis en el rango, por ejemplo, 0.05 mg/kg a 25 mg/kg de peso corporal. No obstante, se prefiere la administración oral, particularmente en forma de tableta. Típicamente, formulaciones farmacéuticas unitarias contendrán alrededor de 0.5 mg a 0.5 g de un compuesto de esta invención.

De acuerdo con un aspecto más de la invención se provee un derivado de quinazolina de la Fórmula I, o su sal farmacéuticamente aceptable, como se define anteriormente para uso en un método de

tratamiento del cuerpo animal o humano mediante terapia.

Como se indicó arriba, se sabe que el papel predominante de la tirosina cinasa de no receptor c-Src es regular la motilidad celular que se requiere necesariamente para que un tumor localizado pase por las etapas de diseminación en el torrente sanguíneo, invasión de otros tejidos e iniciación del crecimiento neoplásico metastásico. Hemos hallado que los derivados de quinazolina de la presente invención poseen potente actividad anti-neoplásica, que se cree se obtiene mediante la inhibición de una o más de las proteína cinasas específicas de la tirosina de no receptor, tales como la cinasa c-Src, las cuales se encuentran involucradas en los pasos de transducción de señales que llevan a la invasividad y capacidad migratoria de las células cancerosas metastásicas.

En consecuencia, los derivados de quinazolina de la presente invención son útiles como agentes anti-neoplásicos, en particular como inhibidores selectivos de la motilidad, diseminación e invasividad de las células cancerosas de mamíferos, los cuales llevan a la inhibición del crecimiento neoplásico metastásico. Particularmente, los derivados de quinazolina de la presente invención son útiles como agentes anti-invasivos en la contención y/o tratamiento de enfermedad de tumor sólido. Particularmente, se espera que los compuestos de la presente invención sean útiles en la prevención o tratamiento de aquellos tumores que son sensibles a la inhibición de una o más de las múltiples tirosina cinasas de no receptor, tales como la cinasa c-Src, que se encuentran involucradas en los pasos de transducción de señales, que llevan a la invasividad y capacidad migratoria de células tumorales metastásicas. Además, se espera que los compuestos de la presente invención sean útiles en la prevención o tratamiento de aquellos tumores que son mediados solos o en parte por la inhibición de la enzima c-Src, *es decir*, los compuestos pueden utilizarse para producir un efecto inhibidor de la enzima c-Src en un animal de sangre caliente necesitado de tal tratamiento. Específicamente, se espera que los compuestos de la presente invención sean útiles en la prevención o tratamiento de enfermedad de tumor sólido.

139

Así, de acuerdo con este aspecto de la invención se provee un derivado de quinazolina de la Fórmula I, o su sal farmacéuticamente aceptable, como se define anteriormente para uso como agente anti-invasivo en la contención y/o tratamiento de enfermedad de tumor sólido.

De acuerdo con una característica adicional de este aspecto de la invención se provee el uso de un derivado de quinazolina de la Fórmula I, o su sal farmacéuticamente aceptable, como se define anteriormente en la manufactura de un medicamento para uso como agente anti-invasivo en la contención y/o tratamiento de enfermedad de tumor sólido.

De acuerdo con una característica adicional de este aspecto de la invención se provee un método para producir un efecto anti-invasivo por la contención y/o tratamiento de enfermedad de tumor sólido en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un derivado de quinazolina de la Fórmula I, o su sal farmacéuticamente aceptable, como se define anteriormente.

De acuerdo con un aspecto más de la invención se provee el uso de un derivado de quinazolina de la Fórmula I, o su sal farmacéuticamente aceptable, como se define anteriormente en la manufactura de un medicamento para uso en la prevención o tratamiento de enfermedad de tumor sólido en un animal de sangre caliente, tal como el hombre.

De acuerdo con una característica adicional de este aspecto de la invención se provee un método para la prevención o tratamiento de enfermedad de tumor sólido en un animal de sangre caliente, tal como el hombre, necesitado de tal tratamiento, que comprende administrar a dicho animal una cantidad efectiva of un derivado de quinazolina de la Fórmula I, o su sal farmacéuticamente aceptable, como se define anteriormente.

De acuerdo con un aspecto más de la invención se provee el uso de un derivado de quinazolina de la Fórmula I, o su sal farmacéuticamente aceptable, como se define anteriormente, en la manufactura de un medicamento para uso en la prevención o tratamiento de aquellos tumores que son sensibles a la inhibición de tirosina cinasas de no receptor, tales

140

como la cinasa c-Src, que se encuentran involucradas en los pasos de transducción de señales, que llevan a la invasividad y capacidad migratoria de células tumorales metastásicas.

De acuerdo con una característica adicional de este aspecto de la invención se provee un método para la prevención o tratamiento de aquellos tumores que son sensibles a la inhibición de tirosina cinasas de no receptor, tales como la cinasa c-Src, que se encuentran involucradas en los pasos de transducción de señales, que llevan a la invasividad y capacidad migratoria de células tumorales metastásicas, que comprende administrar a dicho animal una cantidad efectiva de un derivado de quinazolina de la Fórmula I, o su sal farmacéuticamente aceptable, como se define anteriormente.

De acuerdo con un aspecto más de la invención se provee el uso de un derivado de quinazolina de la Fórmula I, o su sal farmacéuticamente aceptable, como se define anteriormente en la manufactura de un medicamento para uso en proporcionar un efecto inhibidor de la cinasa c-Src.

El tratamiento anti-neoplásico definido anteriormente puede aplicarse como terapia individual o puede incluir, aparte del derivado de quinazolina de la invención, cirugía o radioterapia o quimioterapia convencional. Tal quimioterapia puede incluir una o más de las siguientes categorías de agentes anti-neoplásicos:-

(i) otros agentes anti-invasivos (por ejemplo inhibidores de metaloproteinasa como marimastat e inhibidores de la función receptor de activador del plasminógeno urocinasa);

(ii) medicamentos antiproliferativos/antineoplásicos y sus combinaciones, como se emplean en la oncología médica, tales como agentes alquilantes (por ejemplo cis-platino, carboplatino, ciclofosfamida, mostaza nitrogenada, melfalán, clorambucil, busulfán y nitrosoureas); antimetabolitos (por ejemplo antifolatos tales como fluoropirimidinas como 5-fluorouracilo y tegafur, raltitrexed, metotrexato, citarabina e hidroxiurea; antibióticos antineoplásicos (por ejemplo antraciclinas como adriamicina, bleomicina, doxorubicina, daunomicina, epirubicina, idarubicina,

mitomicina-C, dactinomicina y mitramicina); agentes antimitóticos (por ejemplo antineoplásicos como vincristina, vinblasina, vindesina y vinorelbina y taxoides como taxol y taxotero); e inhibidores de topoisomerasa (por ejemplo epipodofilotoxinas como etopósido y tenipósido, amsacrina, topotecán y camptotecina);

(iii) agentes citostáticos tales como antioestrógenos (por ejemplo tamoxifeno, fulvestrant, toremifeno, raloxifeno, droloxifeno, yodoxifeno), antiandrógenos (por ejemplo bicalutamida, flutamida, nilutamida y acetato de ciproterona), antagonistas LHRH o agonistas LHRH (por ejemplo goserelina, leuprorelina, buserelina), progestógenos (por ejemplo, acetato de megestrol), inhibidores de aromatasa (por ejemplo, anastrozol, letrozol, vorazol y exemestano) e inhibidores de 5α-reductasa (por ejemplo finasteride);

(iv) inhibidores de la función de factor de crecimiento, por ejemplo tales inhibidores incluyen anticuerpos de factor de crecimiento, anticuerpos de receptor de factor de crecimiento, (por ejemplo el anticuerpo anti-erbb2 trastuzumab [Herceptin™] y el anticuerpo anti-erbb1 cetuximab [C225]), inhibidores de farnesiltransferasa, inhibidores de tirosina cinasa e inhibidores de serina/treonina cinasa, por ejemplo inhibidores de la familia de factor de crecimiento epidérmico (por ejemplo inhibidores de la tirosina cinasa de la familia EGFR tales como N-(3-cloro-4-fluorofenil)-7-metoxi-6-(3-morfolinopropoxi)quinazolin-4-amina (gefitinib, ZD1839), N-(3-etinilfenil)-6,7-bis(2-metoxietoxi)quinazolin-4-amina (erlotinib, OSI-774) y 6-acrilamido-N-(3-cloro-4-fluorofenil)-7-(3-morfolinopropoxi)quinazolin-4-amina (CI 1033)),por ejemplo inhibidores de la familia de factor de crecimiento derivado de plaquetas y por ejemplo inhibidores de la familia de factor de crecimiento de hepatocitos;

(v) agentes antiangiogénicos tales como aquellos que inhiben los efectos del factor de crecimiento endotelial vascular, (por ejemplo el anticuerpo de factor de crecimiento celular endotelial anti-vascular bevacizumab [Avastin™], compuestos como los divulgados en las Solicitudes Internacionales de Patentes WO 97/22596, WO 97/30035, WO 97/32856 y

142

WO 98/13354) y compuestos que funcionan por otros mecanismos (por ejemplo linomide, inhibidores de la función integrina αvβ3 y angiostatina);

(vi) agentes de lesión vascular tales como combretastatina A4 y compuestos divulgados en las Solicitudes Internacionales de Patente WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 y WO 02/08213;

(vii) terapias complementarias, por ejemplo las que se dirigen a las dianas listadas más arriba, tales como ISIS 2503, un complementaria anti-ras;

(viii) enfoques de genoterapia, incluidos por ejemplo, enfoques para reemplazar genes aberrantes tales como p53 aberrante o BRCA1 o BRCA2 aberrante, enfoques GDEPT (terapia de conversión de un profármaco con enzima direccionada por genes ***"gene-directed enzyme pro-drug therapy"***) tales como aquellos que usan cytosina deaminasa, timidina cinasa o un enzima de nitroreductasa bacteriana y enfoques para aumentar la tolerancia del paciente al la quimioterapia o radioterapia, tal como genoterapia de resistencia a múltiples fármacos; y

(ix) enfoques de inmunoterapia, incluidos por ejemplo enfoques ex-vivo e in-vivo para aumentar la inmunogenicidad de células neoplásicas de pacientes, tales como transinfección con citocinas tales como interleucina 2, interleucina 4 o factor estimulante de colonias granulocito-macrófago, enfoques para disminuir la anergia de las células T, enfoques que usan inmunocitos transinfectados tales como células dendríticas transinfectadas con citocina, enfoques que emplean estirpes de células neoplásicas transinfectadas con citocina y enfoques que utilizan anticuerpos anti-idiotípicos.

Tal tratamiento conjunto puede lograrse mediante la formulación simultánea, consecutiva o separada de los componentes individuales del tratamiento. Tales productos de combinación emplean los compuestos de esta invención dentro del rango de formulación descrito anteriormente y el otro agente farmacéuticamente activo dentro de su rango de formulación aprobado.

De acuerdo con este aspecto de la invención se provee un producto

farmacéutico que comprende un derivado de quinazolina de la Fórmula I, como se define anteriormente, y un agente adicional anti-neoplásico, como se define anteriormente, para el tratamiento conjunto del cáncer.

Aunque los compuestos de la Fórmula I son principalmente útiles como agentes terapéuticos para uso en animales de sangre caliente (incluido el hombre), también poseen utilidad siempre que se requiera para inhibir los efectos de c-Src. Por consiguiente, son útiles como estándares farmacológicos para uso en el desarrollo de nuevas pruebas biológicas y en la investigación de nuevos agentes farmacológicos.

La invención se ilustrará ahora en los siguientes Ejemplos en los cuales, por lo general:

(i) las operaciones se llevaron a cabo a temperatura ambiente, *es decir*, en el rango 17 a 25°C y bajo una atmósfera de un gas inerte tal como argón, a menos que se especifique lo contrario;

(ii) las evaporaciones se llevaron a cabo por evaporación rotatoria *in vacuo* y se realizaron procedimientos de desarrollo (***"work-up procedures"***) luego de la eliminación de los residuos sólidos por filtración;

(iii) cromatografía de columna (por el procedimiento de destello) y cromatografía líquida de presión media (MPLC) se efectuaron en sílice Merck Kieselgel (Art. 9385) o sílice de fase reversa Merck Lichroprep RP-18 (Art. 9303) obtenido de E. Merck, Darmstadt, Alemania o cromatografía líquida de alta presión (HPLC) realizada en sílice de fase reversa C18, por ejemplo en una columna de fase reversa preparativa Dynamax C-18 60Å;

(iv) los rendimientos, donde se presentan, no son necesariamente los máximos obtenibles;

(v) en general, los productos finales de la Fórmula I tienen microanálisis satisfactorios y sus estructuras se confirmaron por resonancia magnética nuclear (NMR) y/o técnicas de espectro de masa; los datos de espectro de masa con bombardeo rápido de átomos (FAB) se obtuvieron usando un espectrómetro Platform y, donde fuera apropiado, se recogieron datos de iones positivos o datos de iones negativos; los valores de cambio químico NMR se midieron en la escala delta [los espectros de resonancia

144

magnética de protones se determinaron usando un espectrómetro Jeol JNM EX 400 que operaba con una fuerza de campo de 400MHz, un espectrómetro Varian Gemini 2000 que operaba con una fuerza de campo de 300MHz o un espectrómetro Bruker AM300 que operaba con una fuerza de campo de 300MHz]; se han usado las siguientes abreviaturas: s, singlete; d, doblete; t, triplete; q, cuartete; m, multiplete; br, amplio;

(vi) por lo general los intermedios no se caracterizaron completamente y la pureza se evaluó por cromatografía de capa delgada, HPLC, análisis infrarrojo (IR) y/o NMR;

(vii) no se corrigieron los puntos de fusión y se determinaron usando un aparato de punto de fusión automático Mettler SP62 o un aparato de baño de aceite; los puntos de fusión de los productos finales de la Fórmula I se determinaron luego de la cristalización de un disolvente orgánico convencional tal como etanol, metanol, acetona, éter o hexano, solos o en mezcla;

(viii) donde ciertos compuestos se obtuvieron como una sal de adición de ácido, por ejemplo una sal monoclorhidrato o una sal diclorhidrato, la estequiometría de la sal se basó en el número y naturaleza de los grupos básicos en el compuesto, por lo general no se determinó la estequiometría exacta de la sal, por ejemplo mediante datos de análisis elemental;

(ix) cuando se describe el sustituyente en el grupo amino en la posición 4 del anillo de quinazolina en los Ejemplos que siguen, se ha usado la siguiente nomenclatura química '2,3-metilendioxipirid-4-ilo' mientras que, en la descripción y porciones de las reivindicaciones de la especificación de patente, ese grupo se describe a menudo como un 'grupo 2,3-metilendioxipiridin-4-ilo'; para evitar cualquier tipo de duda, hay que entender que cada uno de estos términos se refiere a un grupo de la fórmula;

(x) se han utilizado las siguientes abreviaturas:-

DMF	N,N-dimetilformamida
DMSO	sulfóxido de dimetilo
THF	tetrahidrofurano

145

DMA N,N-dimetilacetamida

Ejemplo 1

4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(3-cloropropoxi)-6-metoxiquinazolina

Hexametildisilazano de sodio (solución 1M en THF; 0.734 ml) se agregó a una solución de 4-amino-5-cloro-2,3-metilendioxipiridina (0.12 g) en DMF (4 ml) que se había enfriado a 0°C y la mezcla se agitó durante 15 minutos. Se agregó una porción (0.1 g) de 4-cloro-7-(3-cloropropoxi)-6-metoxiquinazolina y la mezcla resultante se agitó y se dejó calentar a temperatura ambiente. La mezcla se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se evaporó y el residuo se dividió en porciones entre cloruro de metileno y una solución de cloruro de amonio acuoso saturado. La fase orgánica se lavó con agua y salmuera, se secó sobre sulfato de magnesio y se evaporó. El residuo se purificó por cromatografía de columna en sílice usando mezclas crecientemente polares de cloruro de metileno y acetato de etilo como eluyente seguido por mezclas crecientemente polares de cloruro de metileno y acetonitrilo. Se obtuvo así el compuesto del título como un espuma blanca (0.11 g); Espectro NMR: ($DMSOd_6$ y CD_3CO_2D) 2.3 (m, 2H), 3.8 (m, 2H), 4.05 (s, 3H), 4.4 (t, 2H), 6.3 (s, 2H), 7.4 (s, 1H), 7.9 (s, 1H), 8.15 (s, 1H), 8.95 (s, 1H); Espectro de Masa: $M+H^+$ 423 y 425.

La 4-amino-5-cloro-2,3-metilendioxipiridina usada como material de partida se preparó como sigue:-

Bromoclorometano (20 ml) se agregó a una mezcla de 5-cloro-2,3-dihidroxipiridina (30 g), carbonato de cesio (100 g) y DMF (300 ml) y la mezcla se agitó y se calentó a 90°C durante 3.5 horas. La mezcla se enfrió a temperatura ambiente y se filtró. El filtrado se evaporó y el residuo se purificó por cromatografía de columna en sílice usando cloruro de metileno como eluyenty. Se obtuvo así 5-cloro-2,3-metilendioxipiridina como un sólido blanco (4.7 g); Espectro NMR: ($DMSOd_6$) 6.25 (s, 2H), 7.5 (s, 1H), 7.65 (s, 1H).

Una mezcla de diisopropilamina (8.2 ml) y THF (100 ml) se enfrió a -70°C y n-butil litio (2.5 M en hexano, 24 ml) se agregó gota a gota. La mezcla se agitó a -70°C durante 20 minutos más. Una solución de 5-cloro-2,3-metilendioxipiridina (4.2 g) en THF (40 ml) se agregó durante 10 minutos y la mezcla de reacción se agitó a -70°C durante 1 hora. Gas de dióxido de carbono seco se hizo burbujear en la mezcla de reacción durante 30 minutos. La mezcla de reacción resultante se dejó calentar a temperatura ambiente. Se agregó agua (20 ml) y el disolvente orgánico se evaporó. El residuo se acidificó a pH 2 por la adición de solución 1N de ácido clorhídrico acuoso. El sólido resultante se aisló y se lavó alternativamente con agua éter dietílico y se secó bajo vacío a 40°C. Se obtuvo así ácido 5-cloro-2,3-metilendioxipiridin-4-carboxílico (3.6 g); ^{13}C Espectro NMR: ($DMSOd_6$) 103, 120, 121, 138, 140, 158, 163.

Una mezcla del material así obtenido, azida de difenilfosforilo (3.6 ml), tert-butanol anhidro (13.5 ml), trietilamina (4.2 ml) y 1,4-dioxano (63 ml) se agitó y se calentó a 100°C durante 3 horas. La mezcla se evaporó y el residuo se dividió en porciones entre acetato de etilo y agua. La fase orgánica se lavó con agua, se secó sobre sulfato de magnesio y se evaporó. El residuo se purificó por cromatografía de columna en sílice usando una mezcla 9:1 de cloruro de metileno y acetato de etilo como eluyente. Se obtuvo así tert-butil 5-cloro-2,3-metilendioxipirid-4-ilcarbamato (3.8 g); Espectro NMR: ($DMSOd_6$) 1.45 (s, 9H), 6.2 (s, 2H), 7.7 (s, 1H), 9.2 (s, 1H).

El material así obtenido se disolvió en cloruro de metileno (35 ml) y la solución se enfrió a 0°C. Se agregó ácido trifluoroacético (15 ml) y la mezcla se agitó a 0°C durante 3 horas. La mezcla se dejó calentar a temperatura ambiente y se agitó durante 16 horas. El disolvente se evaporó y el residuo se diluyó con agua helada y se neutralizó a pH 7 por la adición de solución 2N de hidróxido de sodio acuoso mientras se mantenía la temperatura de la mezcla a 0°C. La mezcla resultante se extrajo con cloruro de metileno y el extracto se secó sobre sulfato de magnesio y se evaporó. El residuo se purificó por cromatografía de columna en sílice usando una mezcla 19:1 de cloruro de metileno y éter dietílico como eluyente. Se

obtuvo así 4-amino-5-cloro-2,3-metilendioxipiridina (2 g); Espectro NMR: ($DMSOd_6$) 6.1 (s, 2H), 6.2 (s, 2H), 7.45 (s, 1H); ^{13}C Espectro NMR: ($DMSOd_6$) 100, 112, 125, 136, 138, 157; Espectro de Masa: $M+H^+$ 173.

La 4-cloro-7-(3-cloropropoxi)-6-metoxiquinazolina usada como material de partida se preparó como sigue:-

Formiato de amonio (45 g) se agregó en porciones durante 1.25 horas a una mezcla agitada de 7-benciloxi-6-metoxi-3,4-dihidroquinazolin-4-ona (Solicitud Internacional de Patente WO 02/16352, Ejemplo 1 de la misma; 20 g), 10% catalizador paladio sobre carbón (3.3 g) y DMF (530 ml) y la mezcla de reacción se agitó durante 30 minutos adicionales. Se retiró el catalizador por filtración y el disolvente se evaporó. Se obtuvo así 7-hidroxi-6-metoxi-3,4-dihidroquinazolin-4-ona (8.65 g); Espectro NMR: ($DMSOd_6$) 3.9 (s, 3H), 7.0 (s, 1H), 7.45 (s, 1H), 7.9 (s, 1H).

Una mezcla del material así obtenido, anhídrido acético (63 ml) y piridina (7.5 ml) se calentó 100°C durante 4.5 horas. La mezcla resultante se dejó reposar a temperatura ambiente durante 16 horas. La mezcla se vertió en una mezcla agitada (400ml) de hielo y agua. El precipitado resultante se aisló y se secó bajo vacío. El análisis reveló que la hidrólisis del grupo acetato en la posición 4 de la quinazolina era incompleta. Por consiguiente la mezcla se hidrolizó aún más con agua (150 ml) y piridina (unas cuantas gotas) a 90°C durante 15 minutos. La mezcla resultante se enfrió a temperatura ambiente y el sólido se recogió por filtración, se lavó con agua y se secó bajo vacío. Se obtuvo así 7-acetoxi-6-metoxi-3,4-dihidroquinazolin-4-ona (7.4 g); Espectro NMR: ($DMSOd_6$) 2.3 (s, 3H), 3.9 (s, 3H), 7.45 (s, 1H), 7.65 (s, 1H), 8.05 (s, 1H).

Una mezcla de una porción (2 g) del material así obtenido, cloruro de tionilo (32 ml) y DMF (5 gotas) se agitó y se calentó a reflujo durante 1.5 horas. La mezcla se enfrió a temperatura ambiente y se evaporó el exceso de cloruro de tionilo. Tolueno se agregó al residuo y se evaporó. El residuo resultante se diluyó con cloruro de metileno (15 ml) y una mezcla 10:1 (80 ml) de metanol y se agregó una solución de hidróxido de amonio acuoso saturado. La mezcla resultante se agitó y se calentó a 80°C durante

10 minutos. La mezcla se enfrió a temperatura ambiente y se evaporó. Se agregó agua al residuo y la mezcla se neutralizó por la adición de solución de ácido clorhídrico acuoso diluído. El precipitado resultante se recogió por filtración y se secó bajo vacío a 35°C durante 16 horas. Se obtuvo así 4-cloro-7-hidroxi-6-metoxiquinazolina (1.65 g); Espectro NMR: ($DMSOd_6$) 4.0 (s, 3H), 7.25 (s, 1H), 7.4 (s, 1H), 8.8 (s, 1H).

Di-tert-butil azodicarboxilato (2.3 g) se agregó en porciones durante unos cuantos minutos a una mezcla agitada de 4-cloro-7-hidroxi-6-metoxiquinazolina (1.65 g), 3-cloropropanol (0.7 ml), trifenilfosfamida (2.6 g) y cloruro de metileno (100 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La mezcla se concentró en un volumen aproximado de 30 ml por evaporación y el residuo se purificó por cromatografía de columna en sílice usando mezclas crecientemente polares de éter de petróleo (b.p. 40-60°C) y acetato de etilo como eluyente. Se obtuvo así 4-cloro-7-(3-cloropropoxi)-6-metoxiquinazolina como un sólido blanco (2 g); Espectro NMR: ($DMSOd_6$) 2.3 (m, 2H), 3.8 (m, 2H), 4.05 (s, 3H), 4.4 (m, 2H), 7.45 (s, 1H), 7.55 (s, 1H), 8.9 (s, 1H).

Ejemplo 2

7-(2-cloroetoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-metoxiquinazolina

Usando un procedimiento análogo al descrito en Ejemplo 1, se hizo reaccionar 4-cloro-7-(2-cloroetoxi)-6-metoxiquinazolina con 4-amino-5-cloro- 2,3-metilendioxipiridina para producir el compuesto del título en 92% de rendimiento; Espectro NMR: ($DMSOd_6$ y CD_3CO_2D) 4.05 (s, 3H), 4.1 (t, 2H), 4.55 (t, 2H), 6.3 (s, 2H), 7.4 (s, 1H), 7.9 (s, 1H), 8.15 (s, 1H), 8.95 (s, 1H); Espectro de Masa: $M+H^+$ 409 y 411.

La 4-cloro-7-(2-cloroetoxi)-6-metoxiquinazolina usada como material de partida se preparó como sigue:-

1,2-Dicloroetano (400 ml) se agregó a una mezcla agitada de 7-hidroxi-6-metoxi-3-pivaloiloximetil-3,4-dihidroquinazolin-4-ona (Solicitud Internacional de Patente WO 02/16352, Ejemplo 2, Nota [4] de la misma;

149

85 g), carbonato de potasio (77 g) y DMF (400 ml) y la mezcla de reacción se calentó 70°C durante 16 horas. La mezcla de reacción se enfrió a temperatura ambiente y se filtró. El filtrado se evaporó y el sólido así obtenido se lavó con agua y se secó sobre pentóxido de fósforo a 50°C. El material así obtenido se purificó por cromatografía de columna en sílice usando mezclas crecientemente polares de cloruro de metileno y acetato de etilo como eluyente. Se obtuvo así 7-(2-cloroetoxi)-6-metoxi-3-pivaloiloximetil-3,4-dihidroquinazolin-4-ona como un sólido blanco (65.6 g); Espectro NMR: ($CDCl_3$) 1.2 (s, 9H), 3.9 (t, 2H), 4.0 (s, 3H), 4.4 (t, 2H), 5.95 (s, 2H), 7.1 (s, 1H), 7.7 (s, 1H), 8.2 (s, 1H); Espectro de Masa: $M+H^+$ 369 y 371.

Una mezcla del material así obtenido y una solución saturada de gas de amoníaco en metanol (1.6 L) se agitó a temperatura ambiente durante 2 días. El disolvente se concentró por evaporación a aproximadamente un cuarto del volumen original y se recogió el precipitado se recogió por filtración y se lavó con éter dietílico. Se obtuvo así 7-(2-cloroetoxi)-6-metoxi-3,4-dihidroquinazolin-4-ona como un sólido blanco (44 g); Espectro NMR: ($DMSOd_6$) 3.9 (s, 3H), 4.05 (t, 2H), 4.4 (t, 2H), 7.15 (s, 1H), 7.45 (s, 1H), 8.0 (s, 1H); Espectro de Masa: M+H 255 y 257.

Una mezcla de una porción (5 g) del material así obtenido, cloruro de tionilo (28 ml) y DMF (0.7 ml) se agitó y se calentó a 80°C durante 1.5 horas. Se evaporó el exceso de cloruro de tionilo se evaporó y se agregó tolueno y se evaporó. El sólido residual se suspendió en una mezcla de hielo y agua y se basificó a un pH 7.5 por la adición de una solución 2N de hidróxido de sodio acuoso seguida por una solución de bicarbonato de sodio acuoso saturado. El sólido resultante se recogió por filtración, se lavó con agua y éter dietílico y se secó sobre pentóxido de fósforo bajo vacío. El material así obtenido se purificó por cromatografía de columna en sílice usando mezclas crecientemente polares de cloruro de metileno y acetonitrilo como eluyente. Se obtuvo así 4-cloro-7-(2-cloroetoxi)-6-metoxiquinazolina (3.06 g); Espectro NMR: ($CDCl_3$) 3.95 (t, 2H), 4.1 (s, 3H), 4.5 (t, 2H), 7.35 (s, 1H), 7.45 (s, 1H), 8.9 (s, 1H); Espectro de Masa:

150

$M+H^+$ 273 y 275.

Ejemplo 3

4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-metoxi-7-[3-(4-prop-2-inilpiperazin-1-il)propoxi]quinazolina

Una mezcla de 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(3-cloropropoxi)-6-metoxiquinazolina (0.08 g), 1-prop-2-inilpiperazina (0.047 g), yoduro de potasio (0.01 g) y DMA (2 ml) se agitó y se calentó a 80°C durante 3.5 horas. El disolvente se evaporó y el residuo se dividió en porciones entre cloruro de metileno y una solución de cloruro de amonio acuoso saturado. La fase orgánica se secó sobre sulfato de magnesio y se evaporó. El residuo se purificó por cromatografía de columna en sílice usando una mezcla 19:1 de cloruro de metileno y metanol y luego una mezcla 9:1 de cloruro de metileno y una solución de amoníaco metanólico saturado como eluyente. La goma resultante se trituró bajo éter dietílico. Se obtuvo así el compuesto del título como un sólido (0.066 g); Espectro NMR: (DMSOd_6 y CF_3CO_2D) 2.3 (m, 2H), 3.2-3.6 (br m, 10H), 3.75 (s, 1H), 3.95 (br s, 2H), 4.0 (s, 3H), 4.35 (m, 2H), 6.3 (s, 2H), 7.4 (s, 1H), 7.9 (s, 1H), 8.15 (s, 1H), 8.95 (s, 1H); Espectro de Masa: $M+H^+$ 511 y 513.

La 1-prop-2-inilpiperazina usada como material de partida se preparó como sigue:-

Bromuro de propargilo (solución al 80% en tolueno; 40 ml) se agregó gota a gota durante 10 minutos a una mezcla agitada de 1-tert-butoxicarbonilpiperazina (50 g), carbonato de potasio (74.2 g) y acetonitrilo (2 L) que se había enfriado a 0°C. La mezcla se agitó durante 1.5 horas y se dejó calentar a temperatura ambiente. La mezcla se filtró y el filtrado se evaporó. El residuo se purificó por cromatografía de columna en sílice usando mezclas crecientemente polares de cloruro de metileno y acetato de etilo como eluyente. Se obtuvo así tert-butil 4-prop-2-inilpiperazin-1-carboxilato como un aceite (45.5 g); Espectro NMR: ($CDCl_3$) 1.4 (s, 9H), 2.2 (s, 1H), 2.45 (m, 4H), 3.3 (s, 2H), 3.45 (m, 4H).

Una solución del material así obtenido en cloruro de metileno (100

ml) se agregó lentamente a una solución de gas de cloruro de hidrógeno en 1,4-dioxano (4M, 450 ml). La reacción fue ligeramente exotérmica y se formó un precipitado a medida que se desarrolló gas de dióxido de carbono. La mezcla se agitó a temperatura ambiente durante 1 hora. La mezcla resultante se evaporó y el residuo se suspendió en cloruro de metileno. Una solución de gas de amoníaco en metanol (7M, 110 ml) se agregó y la mezcla se agitó a temperatura ambiente durante 15 minutos. La mezcla se filtró y el filtrado se evaporó. Se obtuvo un aceite el cual cristalizó al reposar. Se obtuvo así 1-prop-2-inilpiperazina (23 g); Espectro NMR: ($CDCl_3$) 2.2 (s, 1H), 2.5 (br s, 4H), 2.85 (m, 4H), 3.25 (s, 2H).

Ejemplo 4

7-(2-cloroetoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-tetrahidropiran-4-iloxiquinazolina

Usando un procedimiento análogo al descrito en Ejemplo 1, 4-cloro-7-(2-cloroetoxi)-5-tetrahidropiran-4-iloxiquinazolina se hizo reaccionar con 4-amino-5-cloro-2,3-metilendioxipiridina para producir el compuesto del título en 37% de rendimiento; Espectro NMR: ($CDCl_3$) 2.0 (m, 2H), 2.3 (m, 2H), 3.65 (m, 2H), 3.9 (m, 2H), 4.1 (m, 2H), 4.4 (m, 2H), 4.8 (m, 1H), 6.2 (s, 2H), 6.65 (s, 1H), 6.9 (s, 1H), 7.8 (s, 1H), 8.6 (s, 1H), 9.5 (s, 1H); Espectro de Masa: $M+H^+$ 479 y 481.

La 4-cloro-7-(2-cloroetoxi)-5-tetrahidropiran-4-iloxiquinazolina usada como material de partida se preparó como sigue:-

Di-tert-butil azodicarboxilato (0.338 g) se agregó a una mezcla agitada de 4-cloro-7-hidroxi-5-tetrahidropiran-4-iloxiquinazolina (Solicitud Internacional de Patente WO01/94341, Ejemplo 15, Nota [10] de la misma; 0.25 g), 2-cloroetanol (0.073 ml), trifenilfosfamida (0.385 g) y cloruro de metileno (15 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 1 hora. La mezcla se concentró en un volumen aproximado de 5 ml por evaporación y el residuo se purificó por cromatografía de columna en sílice usando mezclas crecientemente polares éter de petróleo (b.p. 40-60°C) y acetato de etilo como eluyente. Se obtuvo así 4-cloro-7-(2-

cloroetoxi)-5-tetrahidropiran-4-iloxiquinazolina como un sólido (0.17 g); Espectro NMR: ($CDCl_3$) 2.0 (m, 2H), 2.15 (m, 2H), 3.7 (m, 2H), 3.95 (t, 2H), 4.1 (m, 2H), 4.4 (t, 2H), 4.8 (m, 1H), 6.7 (s, 1H), 6.95 (s, 1H), 8.85 (s, 1H).

Ejemplo 5

7-(2-cloroetoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxiquinazolina

Usando un procedimiento análogo al descrito en Ejemplo 1, 4-cloro-7-(2-cloroetoxi)-5-isopropoxiquinazolina se hizo reaccionar con 4-amino-5-cloro-2,3-metilendioxipiridina para producir el compuesto del título en 86% de rendimiento; Espectro NMR: ($CDCl_3$) 1.55 (d, 6H), 3.9 (t, 2H), 4.4 (t, 2H), 4.9 (m, 1H), 6.2 (s, 2H), 6.6 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.65 (s, 1H); Espectro de Masa: $M+H^+$ 437 y 439.

La 4-cloro-7-(2-cloroetoxi)-5-isopropoxiquinazolina usada como material de partida se preparó como sigue:-

Di-tert-butil azodicarboxilato (28.9 g) se agregó a una mezcla agitada de 7-benciloxi-5-hidroxi-3-pivaloiloximetil-3,4-dihidroquinazolin-4-ona (Solicitud Internacional de Patente WO 01/94341, Ejemplo 15, Nota [8] de la misma; 30 g), isopropanol (7.3 ml), trifenilfosfamida (32.95 g) y cloruro de metileno (350 ml) que se había enfriado a 0°C. La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 1.5 horas. La mezcla se evaporó y el residuo se purificó por cromatografía de columna en sílice usando mezclas crecientemente polares de cloruro de metileno y metanol como eluyente. Se obtuvo así 7-benciloxi-5-isopropoxi-3,4-dihidroquinazolin-4-ona como un sólido (23.8 g); Espectro NMR: ($DMSOd_6$) 7.89 (s, 1H), 7.5-7.3 (m, 5H), 6.75 (s, 1H), 6.62 (s, 1H), 5.24 (s, 2H), 4.65 (m, 1H), 1.29 (d, 6H).

Formiato de amonio (48.4 g) se agregó a una mezcla agitada de 7-benciloxi-5-isopropoxi-3,4-dihidroquinazolin-4-ona (23.8 g), 10% catalizador paladio sobre carbón (2.8 g) y DMF (300 ml) y la mezcla resultante se agitó a temperatura ambiente durante 2 horas. La mezcla se

filtró y el filtrado se evaporó. El material así obtenido se trituró bajo agua, cuyo pH se ajustó a pH 7. El sólido así obtenido se recogió por filtración, se lavó con agua y con éter dietílico y se secó sobre pentóxido de fósforo bajo vacío. Se obtuvo así 7-hidroxi-5-isopropoxi-3,4-dihidroquinazolin-4-ona como un sólido blanco (15.9 g); Espectro NMR: ($DMSOd_6$) 1.3 (d, 6H), 4.57 (m, 1H), 6.42 (s, 1H), 6.5 (s, 1H), 7.8 (s, 1H).

Una mezcla del material así obtenido, anhídrido acético (34 ml) y piridina (0.62 ml) se calentó 70°C durante 30 minutos. La mezcla de reacción se enfrió a temperatura ambiente y se evaporó el exceso de anhídrido acético. El sólido blanco así obtenido se agregó a agua caliente (80°C, 250 ml) y la mezcla se agitó vigorosamente y se calentó a 80°C durante 20 minutos. La mezcla se enfrió a temperatura ambiente y el sólido se aisló y se secó sobre pentóxido de fósforo. Se obtuvo así 7-acetoxi-5-isopropoxi-3,4-dihidroquinazolin-4-ona (17.86 g); Espectro NMR: ($DMSOd_6$) 7.97 (s, 1H), 6.91 (s, 1H), 6.85 (s, 1H), 4.65 (m, 1H), 2.32 (s, 3H), 1.33 (d, 6H).

Una mezcla de una porción (5.4 g) del material así obtenido, trifenilfosfamida (10.8 g), tetracloruro de carbono (12 ml) y 1,2-dicloroetano (50 ml) se agitó y se calentó a 70°C durante 2 horas. La mezcla se enfrió a temperatura ambiente y el disolvente se evaporó. El residuo se disolvió en una solución 0.5M de gas de amoníaco en 1,4-dioxano (250 ml) y la mezcla se calentó 70°C durante 10 minutos. El disolvente se evaporó y el residuo se enfrió en un baño de agua helada. Se agregaron cloruro de metileno y agua y la capa acuosa se llevá a pH 7 por la adición de ácido clorhídrico acuoso diluído. La mezcla se filtró. La fase orgánica se secó sobre sulfato de magnesio y se evaporó para producir 4-cloro-7-hidroxi-5-isopropoxiquinazolina como una espuma la cual se usó sin más purificación.

Di-tert-butil azodicarboxilato (7.9 g) se agregó a una mezcla agitada de la 4-cloro-7-hidroxi-5-isopropoxiquinazolina así obtenida, 2-cloroetanol (1.5 ml), trifenilfosfamida (8 g) y cloruro de metileno (200 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 4 horas. La mezcla se

concentró por evaporación y el residuo se purificó por cromatografía de columna en sílice usando mezclas crecientemente polares de éter de petróleo (b. p. 40-60°C) y acetato de etilo como eluyente. Se obtuvo así 4-cloro-7-(2-cloroetoxi)-5-isopropoxiquinazolina (2.5 g); Espectro NMR: ($CDCl_3$) 1.45 (d, 6H), 3.9 (t, 2H), 4.4 (t, 2H), 4.75 (m, 1H), 6.65 (s, 1H), 6.9 (s, 1H), 8.8 (s, 1H).

Ejemplo 6

Usando un procedimiento análogo al descrito en Ejemplo 3, la 7-haloalcoxiquinazolina apropiada se hizo reaccionar con el compuesto heterocíclico adecuado para producir los compuestos descritos en Tabla I. A menos que se especifique lo contrario, cada compuesto descrito en Tabla I se obtuvo como una base libre.

Tabla 1

Compuesto No. & Nota	$(R^1)_m$	$(R^3)_n$
[1]	6-metoxi-7-[3-(4-isobutirilpiperazin-1-il)propoxi]	5-cloro
[2]	6-metoxi-7-3-[4-(2,2,2-trifluoroetil)piperazin-1-il]propoxi}	5-cloro
[3]	6-metoxi-7-[2-(4-prop-2-inilpiperazin-1 -il)etoxi]	5-cloro
[4]	5-tetrahidropiran-4-iloxi-7-[2-(4-acetilpiperazin-1-il)etoxi]	5-cloro
[5]	5-tetrahidropiran-4-iloxi-7-{2-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]etoxi}	5-cloro
[6]	5-isopropoxi-7-[2-(4-acetilpiperazin-1-il)etoxi]	5-cloro
[7]	5-isopropoxi-7-{2-[(3RS,4SR)-3,4-metilendioxipirrolidin-4-il]etoxi}	5-cloro
[8]	6-(2-morfolinoetoxi)-7-metoxi	5-cloro
[9]	6-[2-(4-metilpiperazin-1-il)etoxi]-7-metoxi	5-cloro
[10]	6-(2-pirrolidin-1-iletoxi)-7-metoxi	5-cloro
[11]	6-[2-(4-acetilpiperazin-1-il)etoxi]-7-metoxi	5-cloro

155

[12]	6-{2-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il] etoxi}-7-metoxi	5-cloro
[13]	6-(3-pirrolidin-1-ilpropoxi)-7-metoxi	5-cloro
[14]	6-(3-morfolinopropoxi)-7-metoxi	5-cloro
[15]	6-[3-(4-acetilpiperazin-1-il)propoxi]-7-metoxi	5-cloro
[16]	6-[3-(4-metilpiperazin-1-il)propoxi]-7-metoxi	5-cloro
[17]	6-{3-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]propoxi}-7-metoxi	5-cloro
[18]	5-tetrahidropiran-4-iloxi-7-[2-(4-prop-2-inilpiperazin-1-il)etoxi]	5-cloro
[19]	5-tatrahidropiran-4-iloxi-7-(2-morfolinoetoxi)	5-cloro
[20]	5-tetrahidropiran-4-iloxi-7-(3-morfolinopropoxi)	5-cloro
[21]	5-tetrahidropiran-4-iloxi-7-[3-(4-prop-2-inilpiperazin-1-il)propoxi]	5-cloro
[22]	5-isopropoxi-7-(2-piperazin-1-iletoxi)	5-cloro
[23]	5-isopropoxi-7-{2-[4-(2-hidroxietil)piperazin-1-il]etoxi}	5-cloro
[24]	5-isopropoxi-7-(2-pirrolidin-1-iletoxi)	5-cloro
[25]	5-isopropoxi-7-(2-piperidinoetoxi)	5-cloro
[26]	5-isopropoxi-7-(2-morfolinoetoxi)	5-cloro
[27]	5-isopropoxi-7-[2-(4-prop-2-inilpiperazin-1-il) etoxi]	5-cloro
[28]	5-isopropoxi-6-{2-[(3RS,4SR)-3,4-dimetoxipirrolidin-1-il]etoxi}	5-cloro
[29]	6-{2-[(3RS,4SR)-3,4-etilidendioxipirrolidin-1-il]etoxi}-5-isopropoxi	5-cloro
[30]	5-isopropoxi-7-[2-(4-metilpiperazin-1-il)etoxi]	5-cloro
[31]	5-isopropoxi-7-(3-morfolinopropoxi)	5-cloro
[32]	7-(3-morfolinopropoxi)	5-cloro
[33]	7-[3-(4-acetilpiperazin-1-il)propoxi]	5-cloro
[34]	6-metoxi-7-[2-(4-prop-2-inilpiperazin-1-il)etoxi]	hidrógeno
[35]	6-metoxi-7-[3-(4-prop-2-inilpiperazin-1-il)propoxi]	hidrógeno

Notas

[1] Los reactivos fueron 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-

156

(3-cloropropoxi)-6-metoxiquinazolina y 1-isobutirilpiperazina. La mezcla de reacción se calentó 120°C durante 3 horas. El producto de reacción se purificó por cromatografía de columna en una columna de sílice de fase reversa C18 (columna Waters Symmetry, sílice de 5 micrones, 19 mm diámetro, 100 mm longitud) usando una mezcla decrecientemente polar de agua y acetonitrilo (que contenía ácido acético al 1%) como eluyente. El material así obtenido se disolvió en cloruro de metileno y se agregó una resina de intercambio de iones (resina de dietilaminopoliestireno, 4 equivalentes) y la mezcla se agitó durante 30 minutos. La mezcla se filtró y el filtrado se evaporó. El residuo resultante se trituró bajo pentano para producir el producto requerido en 51% de rendimiento el cual produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$) 1.1 (d, 6H), 2.1 (m, 2H), 2.45 (m, 4H), 2.55 (m, 2H), 2.75 (m, 1H), 3.5 (m, 2H), 3.6 (m, 2H), 4.0 (s, 3H), 4.25 (t, 2H), 6.1 (s, 2H), 7.1 (br s, 1H), 7.3 (s, 1H), 7.75 (s, 1H), 8.7 (br s, 1H); Espectro de Masa: $M+H^+$ 543 y 545.

La 1-isobutirilpiperazina usada como material de partida se preparó como sigue:-

Cloruro de isobutirilo (3.25 ml) se agregó gota a gota a una mezcla agitada de 1-bencilpiperazina (5 g), trietilamina (4.35 ml) y cloruro de metileno (75ml) la cual se enfrió a 0°C. La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 1 hora. La mezcla se dividió en porciones entre cloruro de metileno y agua. La fase orgánica se lavó con agua y salmuera, se secó sobre sulfato de magnesio y se evaporó. El residuo se purificó por cromatografía de columna en sílice usando una mezcla 3:2 de cloruro de metileno y acetato de etilo como eluyente. Se obtuvo así 1-bencil-4-isobutirilpiperazina (5.95 g) como un aceite; Espectro NMR: ($CDCl_3$) 1.1 (d, 6H), 2.45 (m, 4H), 2.8 (m, 1H), 3.5 (m, 4H), 3.65 (m, 2H), 7.3 (m, 5H); Espectro de Masa: M+H 247.

Una mezcla del material así obtenido, ciclohexeno (70 ml), catalizador de óxido de paladio en carbón (20%; 1.1 g) y etanol (120 ml) se agitó y se calentó a 80°C durante 3 horas. Se retiró el catalizador por filtración y el disolvente se evaporó para producir 1-isobutirilpiperazina

157

(3.7 g) como un sólido; Espectro NMR: ($CDCl_3$) 1.05 (d, 6H), 2.75 (m, 1H), 2.8 (m, 4H), 3.45 (m, 2H), 3.55 (m, 2H).

[2] Los reactivos fueron 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(3-cloropropoxi)-6-metoxiquinazolina y 1-(2,2,2-trifluoroetil)piperazina. La mezcla de reacción se calentó a 120°C durante 3 horas. El producto de reacción se purificó por cromatografía de columna en una columna de sílice de fase reversa C18 (columna Waters Symmetry, sílice de 5 micrones, 19 mm diámetro, 100 mm longitud) usando una mezcla decrecientemente polar de agua y acetonitrilo (que contenía ácido acético al 1%) como eluyente. El material así obtenido se disolvió en cloruro de metileno y en una resina de intercambio de iones (resina de dietilaminopoliestireno, 4 equivalentes) se agregó y la mezcla se agitó durante 30 minutos. La mezcla se filtró y el filtrado se evaporó. El residuo resultante se trituró bajo pentano para producir el producto requerido en 72% de rendimiento el cual produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$) 2.1 (m, 2H), 2.5 (m, 6H), 2.7 (m, 4H), 2.95 (q, 2H), 4.05 (s, 3H), 4.25 (t, 2H), 6.1 (s, 2H), 7.1 (br s, 1H), 7.3 (s, 1H), 7.75 (s, 1H), 8.35 (br s, 1H); Espectro de Masa: $M+H^+$ 555 y 557; Análisis Elemental: Hallado C, 51.8; H, 5.0; N, 14.8; $C_{24}H_{26}ClF_3N_6O_4$ requiere C, 51.9; H, 4.7; N, 15.1%.

La 1-(2,2,2-trifluoroetil)piperazina usada como material de partida se preparó como sigue:-

2,2,2-Trifluoroetil trifluorometansulfonato (8.2 g) se agregó a una mezcla agitada de 1-tert-butoxicarbonilpiperazina (6 g), carbonato de potasio (5.77 g) y acetonitrilo (30 ml) y la mezcla resultante se agitó a temperatura ambiente durante 16 horas. La mezcla se filtró y el filtrado se evaporó. El residuo se purificó por cromatografía de columna en sílice usando mezclas crecientemente polares de éter de petróleo (b.p. 40-60°C) y acetato de etilo como eluyente. Se obtuvo así tert-butil 4-(2,2,2-trifluoroetilpiperazin-1-carboxilato como un sólido (8.1 g); Espectro NMR: ($CDCl_3$) 1.45 (s, 9H), 2.6 (m, 4H), 2.95 (q, 2H), 3.4 (m, 4H).

Gas de cloruro de hidrógeno se hizo burbujear a través de una solución de tert-butil 4-(2,2,2-trifluoroetilpiperazin-1-carboxilato (8 g) en

158

acetato de etilo (50 ml) durante 1.5 horas. Se formó un precipitado a medida que se desarrollaba gas de dióxido de carbono. El precipitado se recogió por filtración, se lavó con acetato de etilo y se secó bajo vacío. Se obtuvo así clorhidrato de 1-(2,2,2-trifluoroetil)piperazina (7 g); Espectro NMR: (DMSOd_6 y CF_3CO_2D) 2.85 (m, 4H), 3.1 (m, 4H), 3.35 (q, 2H).

El material así obtenido se suspendió en cloruro de metileno y se agregó una solución de amoníaco metanólico saturado (20 ml). La mezcla resultante se agitó a temperatura ambiente durante 20 minutos. La mezcla se filtró y el filtrado se evaporó a temperatura ambiente bajo vacío. Se obtuvo así 1-(2,2,2-trifluoroetil)piperazina que se utilizó sin ninguna purificación adicional.

[3] Los reactivos fueron 7-(2-cloroetoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-metoxiquinazolina y 1-prop-2-inilpiperazina. El producto requerido así obtenido en 52% de rendimiento produjo los siguientes datos característicos; Espectro NMR: (DMSOd_6 y CF_3CO_2D) 3.3 (br s, 4H), 3.6 (br s, 4H), 3.75 (br s, 3H), 3.95 (s, 2H), 4.05 (s, 3H), 4.65 (t, 2H), 6.3 (s, 2H), 7.5 (s, 1H), 7.9 (s, 1H), 8.2 (s, 1H), 9.0 (s, 1H); Espectro de Masa: $M+H^+$ 497 y 499; Análisis Elemental: Hallado C, 56.3; H, 5.4; N, 16.2; $C_{24}H_{25}ClN_6O_4$ $0.7H_2O$ requiere C, 56.6; H, 5.2; N, 16.5%.

[4] Los reactivos fueron 7-(2-cloroetoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-tetrahidropiran-4-iloxiquinazolina y 1-acetilpiperazina. La mezcla de reacción se calentó 80°C durante 3 horas y luego a 110°C durante 5 horas. El producto de reacción se purificó por cromatografía de columna en una columna de sílice de fase reversa C18 (Columna Waters Symmetry, sílice de 5 micrones, 19 mm diámetro, 100 mm longitud) usando una mezcla decrecientemente polar de agua y acetonitrilo (que contenía ácido acético al 1%) como eluyente. Los disolventes orgánicos se evaporaron y el pH de la fase acuosa se ajustó a 7.5. La solución se extrajo con cloruro de metileno y la fase orgánica se secó sobre sulfato de magnesio y se evaporó. El residuo resultante se trituró bajo éter dietílico para producir el producto requerido en 45% de rendimiento el cual produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$) 2.0 (m, 2H), 2.1 (s, 3H), 2.3 (m,

159

2H), 2.6 (m, 4H), 2.95 (m, 2H), 3.55 (m, 2H), 3.65 (m, 4H), 4.1 (m, 2H), 4.3 (m, 2H), 4.8 (m, 1H), 6.2 (s, 2H), 6.6 (s, 1H), 6.9 (s, 1H), 7.8 (s, 1H), 8.65 (s, 1H), 9.5 (s, 1H); Espectro de Masa: $M+H^+$ 571 y 573; Análisis Elemental: Hallado C, 55.3; H, 5.4; N, 13.9;$C_{27}H_{31}ClN_6O_6$ $1H_2O$ requiere C, 55.1; H, 5.7; N, 14.3.

[5] Los reactivos fueron 7-(2-cloroetoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-tetrahidropiran-4-iloxiquinazolina y (3RS,4SR)-3,4-metilendioxipirrolidina. La mezcla de reacción se calentó 80°C durante 3 horas y luego a 110°C durante 5 horas. El producto de reacción se purificó por cromatografía de columna en una columna de sílice de fase reversa C18 (Columna Waters Symmetry, sílice de 5 micrones, 19 mm diámetro, 100 mm longitud) usando una mezcla decrecientemente polar de agua y acetonitrilo (que contenía ácido acético al 1%) como eluyente. Los disolventes orgánicos se evaporaron y el pH de la fase acuosa se ajustó a 7.5. La solución se extrajo con cloruro de metileno y la fase orgánica se secó sobre sulfato de magnesio y se evaporó. El residuo resultante se trituró bajo éter dietílico para producir el producto requerido en 69% de rendimiento el cual produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$) 2.0 (m, 2H), 2.3 (m, 2H), 2.4 (m, 2H), 2.3 (t, 2H), 3.3 (d, 2H), 3.55 (m, 2H), 4.1 (m, 2H), 4.3 (t, 2H), 4.65 (m, 2H), 4.8 (m, 1H), 4.9 (s, 1H), 5.2 (s, 1H), 6.2 (s, 2H), 6.6 (s, 1H), 6.9 (s, 1H), 7.8 (s, 1H), 8.65 (s, 1H), 9.5 (s, 1H); Espectro de Masa: $M+H^+$ 558 y 560; Análisis Elemental: Hallado C, 56.5; H, 5.3; N, 12.5; $C_{26}H_{28}ClN_5O_7$ $0.2Et_2O$ requiere C, 56.2; H, 5.3; N, 12.2%.

La (3RS,4SR)-3,4-metilendioxipirrolidina usada como material de partida se preparó como sigue:-

Una solución de di-tert-butil dicarbonato (Boc_2O, 78.95 g) en acetato de etilo (125 ml) se agregó gota a gota a una mezcla agitada de 3-pirrolina (25 g; que contenía pirrolidina 65% pura) y acetato de etilo (125 ml) que se había enfriado a 0°C. La temperatura de reacción se mantuvo a 5-10°C durante la adición. La mezcla de reacción resultante se dejó calentar a temperatura ambiente de un día para otro. La mezcla de reacción se lavó

160

sucesivamente con agua, solución 0.1N de ácido clorhídrico acuoso, agua, una solución de bicarbonato de sodio acuoso saturado y salmuera, se secó sobre sulfato de magnesio y se evaporó. Se obtuvo así, como un aceite incoloro (62 g), una mezcla 2:1 de tert-butil 3-pirrolin-1-carboxilato, NMR: ($CDCl_3$) 1.45 (s, 9H), 4.1 (d, 4H), 6.75 (m, 2H), y tert-butil pirrolidin-1-carboxilato, NMR: ($CDCl_3$) 1.5 (s, 9H), 1.8 (br s, 4H), 3.3 (br s, 4H).

Una solución de la mezcla de los materiales así obtenidos en acetona (500 ml) se agregó gota a gota a una mezcla of N-metilmorfolin-N-óxido (28.45 g), tetraóxido de osmio (1 g) y agua (500 ml) mientras se mantenía la temperatura de reacción por debajo de 25°C. La mezcla de reacción se agitó entonces a temperatura ambiente durante 5 horas. El disolvente se evaporó y el residuo se dividió en porciones entre acetato de etilo y agua. La fase orgánica se lavó con salmuera, se secó sobre sulfato de magnesio y se evaporó. El residuo se purificó por cromatografía de columna en sílice usando mezclas crecientemente polares de éter de petróleo (b.p. 40-60°C) y acetato de etilo como eluyente y mediante cromatografía adicional de columna en sílice usando mezclas crecientemente polares de cloruro de metileno y metanol. Se obtuvo así tert-butil (3RS,4SR)-3,4-dihidroxipirrolidin-1-carboxilato como un aceite (34.6 g); Espectro NMR: ($CDCl_3$) 1.45 (s, 9H), 2.65 (m, 2H), 3.35 (m, 2H), 3.6 (m, 2H), 4.25 (m, 2H).

Una solución de tert-butil (3RS,4SR)-3,4-dihidroxipirrolidin-1-carboxilato (34.6 g) en DMF (400 ml) se enfrió a 0-5°C y se agregó en porciones hidruro de sodio (60% dispersión en aceite mineral, 0.375 mol). La mezcla de reacción se agitó a 5°C durante 1 hora. Se agregó dibromometano (15.6 ml) y la mezcla de reacción se agitó a 5°C durante 30 minutos. La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 16 horas. El DMF se evaporó y el residuo se dividió en porciones entre acetato de etilo y agua. La fase orgánica se lavó con agua y salmuera, se secó sobre sulfato de magnesio y se evaporó. El residuo se purificó por cromatografía de columna en sílice usando mezclas crecientemente polares de éter de petróleo (b.p. 40-60°C) y acetato de etilo

como eluyente. Se obtuvo así tert-butil (3RS,4SR)-3,4-metilendioxipirrolidin-1-carboxilato como un aceite incoloro (19.77g); Espectro NMR: ($CDCl_3$) 1.45 (s, 9H), 3.35 (m, 2H), 3.75 (br s, 2H), 4.65 (m, 2H), 4.9 (s, 1H), 5.1 (s, 1H).

Una solución 5M enfriada de cloruro de hidrógeno en isopropanol (150 ml) se agregó a una solución de tert-butil (3RS,4SR)-3,4-metilendioxipirrolidin-1-carboxilato (19.7 g) en cloruro de metileno (500 ml) que se enfrió en un baño de aceite. La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 4 horas. El disolvente se evaporó y el residuo se trituró bajo éter dietílico. El precipitado se recogió por filtración, se lavó con éter dietílico y se secó. Se obtuvo así clorhidrato de (3RS,4SR)-3,4-metilendioxipirrolidina como un sólido café claro (13.18 g); Espectro NMR: ($DMSOd_6$) 3.15 (m, 2H), 3.35 (m, 2H), 4.65 (s, 1H), 4.8 (m, 2H), 5.1 (s, 1H).

El material así obtenido se suspendió en éter dietílico y se agregó una solución de amoníaco metanólico saturado. La mezcla resultante se agitó a temperatura ambiente durante 10 minutos. La mezcla se filtró y el disolvente se evaporó a temperatura ambiente bajo vacío. Se obtuvo así (3RS,4SR)-3,4-metilendioxipirrolidina la cual se utilizó sin ninguna purificación adicional.

[6] Los reactivos fueron 7-(2-cloroetoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxiquinazolina y 1-acetilpiperazina. La mezcla de reacción se calentó 85°C durante 8 horas. El producto de reacción se purificó por cromatografía de columna en sílice usando mezclas crecientemente polares of cloruro de metileno y metanol como eluyente. El producto así obtenido en 89% de rendimiento produjo los siguientes datos característicos; m.p. 208-210°C; Espectro NMR: ($CDCl_3$) 1.55 (d, 6H), 2.1 (s, 3H), 2.6 (m, 4H), 2.9 (t, 2H), 3.5 (t, 2H), 3.7 (t, 2H), 4.25 (t, 2H), 4.85 (m, 1H), 6.15 (s, 2H), 6.55 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Espectro de Masa: $M+H^+$ 529 y 531; Análisis Elemental: Hallado C, 57.0; H, 5.7; N, 15.7; $C_{25}H_{29}ClN_6O_5$ requiere C, 56.8; H, 5.5; N, 15.9%.

[7] Los reactivos fueron 7-(2-cloroetoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxiquinazolina y (3RS,4SR)-3,4-metilendioxipirrolidina. La mezcla de reacción se calentó a 95°C durante 3 horas. El producto de reacción se purificó por cromatografía de columna en una columna de sílice de fase reversa C18 (Columna Waters Symmetry, sílice de 5 micrones, 19 mm diámetro, 100 mm longitud) usando una mezcla decrecientemente polar de agua y acetonitrilo (que contenía ácido acético al 1%) como eluyente. Se evaporaron los disolventes orgánicos y se ajustó el pH de la fase acuosa a 7. La solución se extrajo con cloruro de metileno y la fase orgánica se secó sobre sulfato de magnesio y se evaporó. El residuo resultante se trituró bajo éter dietílico para producir el producto requerido en 64% de rendimiento el cual produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$) 1.55 (d, 6H), 2.35 (m, 2H), 2.9 (t, 2H), 3.25 (d, 2H), 4.25 (t, 2H), 4.6 (m, 2H), 4.85 (m, 1H), 4.9 (s, 1H), 5.15 (s, 1H), 6.15 (s, 2H), 6.55 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Espectro de Masa: $M+H^+$ 516 y 518; Análisis Elemental: Hallado C, 54.7; H, 5.2; N, 13.2; $C_{24}H_{26}ClN_5O_6$ $0.5H_2O$ requiere C, 54.9; H, 5.2; N, 13.3%.

[8] Los reactivos fueron 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-(2-cloroetoxi)-7-metoxiquinazolina (cuya preparación se describe en Ejemplo 7 más adelante) y morfolina. La mezcla de reacción se calentó a 120°C durante 16 horas. El producto requerido así obtenido en 69% de rendimiento produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$ y CD_3CO_2D) 3.3 (m, 4H), 3.5 (t, 2H), 3.95 (m, 4H), 4.05 (s, 3H), 4.6 (t, 2H), 6.15 (s, 2H), 7.6 (s, 1H), 7.8 (s, 2H), 8.6 (s, 1H); Espectro de Masa: $M+H^+$ 460 y 462; Análisis Elemental: Hallado C, 53.45; H, 4.8; N, 14.5; $C_{21}H_{22}ClN_5O_5$ $0.55H_2O$ requiere C, 53.7; H, 5.0; N, 14.9%.

[9] Los reactivos fueron 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-(2-cloroetoxi)-7-metoxiquinazolina y 1-metilpiperazina. La mezcla de reacción se calentó 120°C durante 16 horas. El producto de reacción se purificó por cromatografía de columna en una columna de sílice Waters X-Terra (de fase reversa C18, 5 micrones, 19 mm diámetro, 100 mm longitud;

163

Waters Inc., Milford, MA01757, USA) y se eluyó con mezclas decrecientemente polares de un tampón de carbonato de amonio (2 g/L en agua) y acetonitrilo. Se recogieron fracciones apropiadas, el disolvente orgánico se evaporó y la mezcla resultante se dividió en porciones entre acetato de etilo y una solución de bicarbonato de sodio acuoso saturado. La fase orgánica se secó sobre sulfato de magnesio y se evaporó. Se obtuvo así el producto requerido en 29% de rendimiento el cual produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$ y CD_3CO_2D) 2.7 (s, 3H), 3.25-3.35 (br m, 10H), 4.05 (s, 3H), 4.45 (t, 2H), 6.15 (s, 2H), 7.55 (s, 1H), 7.7 (s, 1H), 7.8 (s, 1H), 8.65 (s, 1H); Espectro de Masa: $M+H^+$ 473 y 475; Análisis Elemental: Hallado C, 54.9; H, 5.3; N, 17.1; $C_{22}H_{25}ClN_6O_4$ $0.4H_2O$ requiere C, 55.0; H, 5.4; N, 17.5%.

[10] Los reactivos fueron 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-(2-cloroetoxi)-7-metoxiquinazolina y pirrolidina. La mezcla de reacción se calentó a 120°C durante 16 horas. El producto requerido así obtenido en 41% de rendimiento produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$ y CD_3CO_2D) 2.15 (m, 4H), 3.3-3.6 (br s, 4H), 3.7 (t, 2H), 4.05 (s, 3H), 4.65 (t, 2H), 6.15 (s, 2H), 7.65 (s, 1H), 7.8 (s, 1H), 7.9 (s,1H), 8.65 (s, 1H); Espectro de Masa: $M+H^+$ 444 y 446; Análisis Elemental: Hallado C, 55.0; H, 5.0; N, 14.9; $C_{21}H_{22}ClN_5O_4$ $0.7H_2O$ requiere C, 55.25; H, 5.2; N, 15.3%.

[11] Los reactivos fueron 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-(2-cloroetoxi)-7-metoxiquinazolina y1-acetilpiperazina. La mezcla de reacción se calentó a 120°C durante 16 horas. El producto requerido así obtenido en 51% de rendimiento produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$ y CD_3CO_2D) 2.15 (s, 3H), 3.1 (m, 2H), 3.2 (m, 2H), 3.4 (t, 2H), 3.75 (m, 2H), 3.85 (m, 2H), 4.0 (s, 3H), 4.55 (t, 2H), 6.15 (s, 2H), 7.6 (s, 1H), 7.7 (s, 1H), 7.8 (s, 1H), 8.6 (s, 1H); Espectro de Masa: $M+H^+$ 501 y 503.

[12] Los reactivos fueron 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-(2-cloroetoxi)-7-metoxiquinazolina y (3RS,4SR)-3,4-metilendioxipirrolidina. La mezcla de reacción se calentó a 120°C durante 16 horas. El producto

requerido así obtenido en 73% de rendimiento produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$ y CD_3CO_2D) 2.95 (m, 2H), 3.45 (t, 2H), 3.65 (d, 2H), 4.05 (s, 3H), 4.55 (t, 2H), 4.8 (m, 3H), 5.2 (s, 1H), 6.15 (s, 2H), 7.6 (s, 1H), 7.75 (s, 1H), 7.8 (s, 1H), 8.65 (s, 1H); Espectro de Masa: $M+H^+$ 488 y 490.

[13] Los reactivos fueron 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-(3-cloropropoxi)-7-metoxiquinazolina (cuya preparación se describe en Ejemplo 8 más adelante) y pirrolidina. La mezcla de reacción se calentó a 120°C durante 16 horas. El producto requerido así obtenido en 50% de rendimiento produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$ y CD_3CO_2D) 2.1 (m, 4H), 2.4 (m, 2H), 3.0-3.8 (br s, 4H), 3.4 (t, 2H), 4.05 (s, 3H), 4.35 (t, 3H), 6.1 (s, 2H), 7.6 (s, 1H), 7.75 (s, 1H), 7.8 (s, 1H), 8.65 (s, 1H); Espectro de Masa: $M+H^+$ 458 y 460; Análisis Elemental: Hallado C, 57.3; H, 5.4; N, 14.5; $C_{22}H_{24}ClN_5O_4$ $0.15H_2O$ requiere C, 57.4; H, 5.3; N, 15.2%.

[14] Los reactivos fueron 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-(3-cloropropoxi)-7-metoxiquinazolina y morfolina. La mezcla de reacción se calentó a 120°C durante 16 horas. El producto requerido así obtenido en 72% de rendimiento produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$) 2.1 (m, 2H), 2.5 (m, 4H), 2.6 (t, 2H), 3.7 (m, 4H), 4.05 (s, 3H), 4.25 (t, 2H), 6.1 (s, 2H), 7.05 (s, 1H), 7.15 (s, 1H), 7.3 (s, 1H), 7.75 (s, 1H), 8.7 (s, 1H); Espectro de Masa: $M+H^+$ 474 y 476.

[15] Los reactivos fueron 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-(3-cloropropoxi)-7-metoxiquinazolina y 1-acetilpiperazina. La mezcla de reacción se calentó a 120°C durante 16 horas. El producto requerido así obtenido en 39% de rendimiento produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$ y CD_3CO_2D) 2.15 (s, 3H), 2.35 (m, 2H), 3.15-3.3 (m, 6H), 3.8 (m, 2H), 3.9 (m, 2H), 4.0 (s, 3H), 4.3 (t, 2H), 6.15 (s, 2H), 7.6 (s, 1H), 7.65 (s, 1H), 7.8 (s, 1H), 8.65 (s, 1H); Espectro de Masa: $M+H^+$ 515 y 517.

[16] Los reactivos fueron 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-(3-cloropropoxi)-7-metoxiquinazolina y 1-acetilpiperazina. La mezcla de

reacción se calentó a 120°C durante 16 horas. El producto requerido así obtenido en 27% de rendimiento produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$ y CD_3CO_2D) 2.3 (m, 2H), 2.7 (s, 3H), 3.3 (t, 2H), 3.4 (m, 4H), 3.5 (m, 4H), 4.0 (s, 3H), 4.3 (t, 2H), 6.15 (s, 2H), 7.6 (s, 1H), 7.65 (s, 1H), 7.8 (s, 1H), 8.65 (s, 1H); Espectro de Masa: $M+H^+$ 487 y 489.

[17] Los reactivos fueron 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-(3-cloropropoxi)-7-metoxiquinazolina y (3RS,4SR)-3,4-metilendioxipirrolidina. La mezcla de reacción se calentó a 95°C durante 3 horas. El producto de reacción se purificó por cromatografía de columna en una columna de sílice de fase reversa C18 (Columna Waters Symmetry, sílice de 5 micrones, 19 mm diámetro, 100 mm longitud) usando una mezcla decrecientemente polar de agua y acetonitrilo (que contenía ácido acético al 1%) como eluyente. Se evaporaron los disolventes orgánicos y se ajustó el pH de la fase acuosa a 7. La solución se extrajo con cloruro de metileno y la fase orgánica se secó sobre sulfato de magnesio y se evaporó. El residuo resultante se trituró bajo éter dietílico para producir el producto requerido en 57% de rendimiento el cual produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$ y CD_3CO_2D) 2.3 (m, 2H), 3.3 (m, 2H), 3.4 (t, 2H), 3.6 (d, 2H), 4.0 (s, 3H), 4.3 (t, 2H), 4.8 (m, 3H), 5.2 (s, 1H), 6.15 (s, 2H), 7.55 (s, 1H), 7.6 (s, 1H), 7.8 (s, 1H), 8.6 (s, 1H); Espectro de Masa: $M+H^+$ 502 y 504.

[18] Los reactivos fueron 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(2-cloroetoxi)-5-tetrahidropiran-4-iloxiquinazolina y 1-prop-2-inilpiperazina. La mezcla de reacción se calentó a 80°C durante 3 horas y luego a 110°C durante 5 horas. El producto de reacción se purificó por cromatografía de columna en una columna de sílice Waters X-Terra (fase reversa C18, 5 micrones, 19 mm diámetro, 100 mm longitud) y se eluyó con mezclas decrecientemente polares de un tampón de carbonato de amonio (2 g/L en agua) y acetonitrilo. Se recogieron fracciones apropiadas, el disolvente orgánico se evaporó y la mezcla resultante se dividió en porciones entre acetato de etilo y una solución de bicarbonato de sodio acuoso saturado. La

166

fase orgánica se secó sobre sulfato de magnesio y se evaporó. Se obtuvo así el producto requerido en 54% de rendimiento el cual produjo los siguientes datos característicos; Espectro NMR: ($DMSOd_6$ y CD_3CO_2D) 1.85 (m, 2H), 2.15 (m, 2H), 2.5-3.0 (m, 10H), 3.15 (s, 1H), 3.3 (s, 2H), 3.55 (t, 2H), 3.9 (m, 2H), 4.3 (m, 2H), 5.05 (m, 1H), 6.2 (s, 2H), 6.9 (s, 2H), 7.8 (s, 1H), 8.5 (s, 1H); Espectro de Masa: $M+H^+$ 567 y 569; Análisis Elemental: Hallado C, 55.9; H, 5.6; N, 14.0; $C_{28}H_{31}ClN_6O_5$ $2H_2O$ requiere C, 55.8; H, 5.85; N, 13.9%.

[19] Usando las condiciones detalladas descritas en la Nota [18] inmediatamente arriba, 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(2-cloroetoxi)-5-tetrahidropiran-4-iloxiquinazolina se hizo reaccionar con morfolina para producir el producto requerido en 48% de rendimiento el cual produjo los siguientes datos característicos; Espectro NMR: ($DMSOd_6$ y CD_3CO_2D) 1.8 (m, 2H), 2.15 (m, 2H), 2.55 (m, 4H), 2.8 (m, 2H), 3.5 (m, 2H), 3.6 (m, 4H), 3.9 (m, 2H), 4.3 (t, 2H), 5.1 (m, 1H), 6.2 (s, 2H), 6.9 (m, 2H), 7.8 (s, 1H), 8.45 (s, 1H); Espectro de Masa: $M+H^+$ 530 y 532; Análisis Elemental: Hallado C, 51.8; H, 5.8; N, 12.1;$C_{25}H_{28}ClN_5O_6$ $2.5H_2O$ requiere C, 52.2; H, 5.8; N, 12.2%.

[20] Los reactivos fueron 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(3-cloropropoxi)-5-tetrahidropiran-4-iloxiquinazolina (descrita en Ejemplo 9 más adelante) y morfolina. El producto requerido así obtenido en 30% de rendimiento produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$ y CF_3CO_2D) 2.05 (m, 2H), 2.35 (m, 4H), 3.15 (m, 2H), 3.45 (m,2H), 3.75 (m, 4H), 3.9 (m, 2H), 4.2 (m, 6H), 5.0 (m, 1H), 6.3 (s, 2H), 6.85 (s, 1H), 7.0 (s, 1H), 7.9 (s,1H), 8.7 (s, 1H); Espectro de Masa: $M+H^+$ 544 y 546.

[21] Los reactivos fueron 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(3-cloropropoxi)-5-tetrahidropiran-4-iloxiquinazolina y 1-prop-2-inilpiperazina. El producto de reacción se purificó por cromatografía de columna en una columna de sílice de fase reversa C18 (Columna Waters Symmetry, sílice de 5 micrones, 19 mm diámetro, 100 mm longitud) usando una mezcla decrecientemente polar de agua y acetonitrilo (que contenía

ácido acético al 1%) como eluyente. Se evaporaron los disolventes orgánicos y se ajustó el pH de la fase acuosa a 9. La solución se extrajo con cloruro de metileno y la fase orgánica se secó sobre sulfato de magnesio y se evaporó. El residuo resultante se trituró bajo pentano para producir el producto requerido en 48% de rendimiento el cual produjo los siguientes datos característicos; Espectro NMR: ($DMSOd_6$ y CD_3CO_2D) 1.85 (m, 2H), 2.0 (m, 2H), 2.15 (m, 2H), 2.5-2. 8 (br m, 10H), 3.15 (s, 1H), 3.3 (s, 2H), 3.55 (t, 2H), 3.9 (m, 2H), 4.2 (t, 2H), 5.05 (m, 1H), 6.2 (s, 2H), 6.85 (s, 1H), 6.9 (s, 1H), 7.8 (s, 1H), 8.45 (s, 1H); Espectro de Masa: $M+H^+$ 581 y 583.

[22] Los reactivos fueron 7-(2-cloroetoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxiquinazolina y piperazina. El producto requerido así obtenido en 30% de rendimiento produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$) 1.55 (d, 6H), 2.6 (m, 4H), 2.85 (t, 2H), 2.95 (m, 4H), 4.25 (t, 2H), 4.85 (m, 1H), 6.15 (s, 2H), 6.55 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Espectro de Masa: $M+H^+$ 487 y 489; Análisis Elemental: Hallado C, 55.4; H, 5.5; N, 16.4; $C_{23}H_{27}ClN_6O_4$ $0.1Et_2O$ $0.6H_2O$ requiere C, 55.65; H, 5.8; N, 16.6%.

[23] Los reactivos fueron 7-(2-cloroetoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxiquinazolina y 1-(2-hidroxietil)piperazina. La mezcla de reacción se calentó a 85°C durante 8 horas. El producto de reacción se purificó por cromatografía de columna en sílice usando mezclas crecientemente polares de cloruro de metileno y metanol como eluyente. El material así obtenido se trituró bajo éter dietílico para producir el producto requerido en 67% de rendimiento el cual produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$) 1.5 (d, 6H), 2.5-2.7 (br m, 12H), 3.65 (t, 2H), 4.25 (t, 2H), 4.8 (m, 1H), 6.15 (s, 2H), 6.6 (s, 1H), 6.85 (s, 1H), 7.25 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Espectro de Masa: $M+H^+$ 531 y 533; Análisis Elemental: Hallado C, 55.4; H, 6.05; N, 15.2; $C_{25}H_{31}ClN_6O_5$ $0.1Et_2O$ $0.5H_2O$ requiere C, 55.7; H, 6.1; N, 15.35%.

[24] Los reactivos fueron 7-(2-cloroetoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxiquinazolina y pirrolidina. La mezcla de reacción se calentó 80°C durante 4 horas. El producto de reacción se purificó por

168

cromatografía de columna en una columna de sílice de fase reversa C18 (Columna Waters Symmetry, sílice de 5 micrones, 19 mm diámetro, 100 mm longitud) usando una mezcla decrecientemente polar de agua y acetonitrilo (que contenía ácido acético al 1%) como eluyente. Se evaporaron los disolventes orgánicos y se ajustó el pH de la fase acuosa a 9. La solución se extrajo con cloruro de metileno y la fase orgánica se secó sobre sulfato de magnesio y se evaporó. El residuo resultante se trituró bajo pentano para producir el producto requerido en 62% de rendimiento el cual produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$) 1.55 (d, 6H), 1.85 (m, 4H), 2.6 (m, 4H), 2.95 (t, 2H), 4.25 (t, 2H), 4.85 (m, 1H), 6.15 (s, 2H), 6.6 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Espectro de Masa: $M+H^+$ 472 y 474; Análisis Elemental: Hallado C, 58.3; H, 5.4; N, 14.7; $C_{23}H_{26}ClN_5O_4$ requiere C, 58.5; H, 5.55; N, 14.8%.

[25] Usando las condiciones detalladas descritas en la Nota [24] inmediatamente arriba, 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(2-cloroetoxi)-5-tetrahidropiran-4-iloxiquinazolina se hizo reaccionar con piperidina para producir el producto requerido en 52% de rendimiento el cual produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$) 1.45 (m, 2H), 1.55 (d, 6H), 1.65 (m, 4H), 2.5 (m, 4H), 2.85 (t, 2H), 4.25 (t, 2H), 4.85 (m, 1H), 6.15 (s, 2H), 6.6 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Espectro de Masa: $M+H^+$ 486 y 488; Análisis Elemental: Hallado C, 59.3; H, 5.9; N, 14.4; $C_{24}H_{28}ClN_5O_4$ requiere C, 59.3; H, 5.8; N, 14.4%.

[26] Usando las condiciones detalladas descritas en la Nota [24] inmediatamente arriba, 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(2-cloroetoxi)-5-tetrahidropiran-4-iloxiquinazolina se hizo reaccionar con morfolina para producir el producto requerido en 57% de rendimiento el cual produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$) 1.55 (d, 6H), 2.6 (m, 4H), 2.85 (t, 2H), 3.75 (m, 4H), 4.25 (t, 2H), 4.85 (m, 1H), 6.15 (s, 2H), 6.55 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Espectro de Masa: $M+H^+$ 488 y 490; Análisis Elemental: Hallado C, 56.6; H, 5.4; N, 14.2; $C_{23}H_{26}ClN_5O_5$ requiere C, 56.6; H, 5.4; N, 14.35%.

[27] Usando las condiciones detalladas descritas en la Nota [24] inmediatamente arriba, 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(2-cloroetoxi)-5-tetrahidropiran-4-iloxiquinazolina se hizo reaccionar con 1-prop-2-inilpiperazina para producir el producto requerido en 41% de rendimiento el cual produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$) 1.55 (d, 6H), 2.25 (s, 1H), 2.65 (br m, 8H), 2.9 (t, 2H), 3.3 (s, 2H), 4.25 (t, 2H), 4.85 (m, 1H), 6.15 (s, 2H), 6.55 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Espectro de Masa: $M+H^+$ 525 y 527; Análisis Elemental: Hallado C, 59.3; H, 5.4; N, 15.85; $C_{26}H_{29}ClN_6O_4$ requiere C, 59.5; H, 5.6; N, 16.0%.

[28] Los reactivos fueron 7-(2-cloroetoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxiquinazolina y (3RS,4SR)-3,4-dimetoxipirrolidina. El producto requerido así obtenido en 78% de rendimiento produjo los siguientes datos característicos; Espectro NMR: ($DMSOd_6$ y CD_3CO_2D) 1.45 (d, 6H), 2.7 (m, 2H), 3.0 (m, 2H), 3.15 (m, 2H), 3.3 (s, 6H), 3.75 (m, 2H), 4.25 (t, 2H), 5.5 (m, 1H), 6.2 (s, 2H), 6.8 (s, 1H), 6.85 (s, 1H), 7.8 (s, 1H), 8.45 (s, 1H); Espectro de Masa: $M+H^+$ 532 y 534; Análisis Elemental: Hallado C, 56.0; H, 5.6; N, 12.85; $C_{25}H_{30}ClN_5O_6$ $0.3H_2O$ requiere C, 56.25; H, 5.7; N, 13.1%.

La (3RS,4SR)-3,4-dimetoxipirrolidina usada como material de partida se obtuvo como sigue:-

Una solución de tert-butil (3RS,4SR)-3,4-dihidroxipirrolidin-1-carboxilato (1 g) en DMF (20 ml) se enfrió a 0-5°C y se agregó en porciones hidruro de sodio (60% dispersión en aceite mineral, 0.433 g). La mezcla de reacción se agitó a 5°C durante 1 hora. Se agregó yoduro de metilo (0.675 ml) y la mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 16 horas. El DMF se evaporó y el residuo se dividió en porciones entre éter dietílico y agua. La fase orgánica se lavó con agua y salmuera, se secó sobre sulfato de magnesio y se evaporó. El residuo se purificó por cromatografía de columna en sílice usando mezclas crecientemente polares de éter de petróleo (b.p. 40-60°C) y acetato de etilo como eluyente. Se obtuvo así tert-butil (3RS,4SR)-3,4-dimetoxipirrolidin-

1-carboxilato como un aceite (1.06g); Espectro NMR: ($CDCl_3$) 1.45 (s, 9H), 3.35 (m, 1H), 3.45 (s, 6H), 3.5 (m, 2H), 3.55 (m, 1H), 3.85 (m, 2H).

Una solución 5M enfriada de cloruro de hidrógeno en isopropanol (3 ml) se agregó a una solución de tert-butil (3RS,4SR)-3,4-dimetoxipirrolidin-1-carboxilato (1 g) en cloruro de metileno (25 ml) que se enfrió en un baño de aceite. La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 16 horas. El disolvente se evaporó. Se obtuvo así clorhidrato de (3RS,4SR)-3,4-dimetoxipirrolidina como un aceite (0.72 g); Espectro NMR: ($DMSOd_6$) 3.1 (m, 2H), 3.25 (m, 2H), 3.35 (s, 6H), 4.0 (m, 2H), 9.3 (br s, 1H), 9.5 (br s, 1H).

El material así obtenido se disolvió en cloruro de metileno y se agregó una solución 7M de amoníaco metanólico (0.2 ml). La mezcla resultante se agitó a temperatura ambiente durante 5 minutos. La mezcla se filtró y el disolvente se evaporó a temperatura ambiente bajo vacío. Se obtuvo así (3RS,4SR)-3,4-dimetoxipirrolidina la cual se utilizó sin ninguna purificación adicional.

[29] Usando las condiciones detalladas descritas en la Nota [24] inmediatamente arriba, excepto que el producto se trituró bajo éter dietílico más bien que bajo pentano, 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(2-cloroetoxi)-5-tetrahidropiran-4-iloxiquinazolina se hizo reaccionar con (3RS,4SR)-3,4-etilidendioxipirrolidina para producir el producto requerido en 67% de rendimiento el cual produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$) 1.45 (d, 3H), 1.55 (d, 6H), 2.3 (d, 2H), 2.95 (m, 2H), 3.25 (d, 2H), 4.25 (t, 2H), 4.55 (m, 2H), 4.8 (m, 1H), 5.0 (m, 1H), 6.15 (s, 2H), 6.55 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Espectro de Masa: $M+H^+$ 530 y 532; Análisis Elemental: Hallado C, 56.7; H, 5.5; N, 12.9; $C_{25}H_{28}ClN_5O_6$ $0.1Et_2O$ requiere C, 56.8; H, 5.4; N, 13.0%.

La (3RS,4SR)-3,4-etilidendioxipirrolidina usada como material de partida se obtuvo como sigue:-

Una solución de tert-butil (3RS,4SR)-3,4-dihidroxipirrolidin-1-carboxilato (0.5 g) en cloruro de metileno (15 ml) se enfrió a 0-5°C y se agregaron alternativamente acetaldehído dimetilacetal (0.782ml) y ácido 4-

171

toluensulfónico (0.025 g). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La mezcla resultante se evaporó y el residuo se purificó por cromatografía de columna en sílice usando mezclas crecientemente polares de éter de petróleo (b.p. 40-60°C) y acetato de etilo como eluyente. Se obtuvo así tert-butil (3RS,4SR)-3,4-etilidendioxipirrolidin-1-carboxilate como un aceite (0.484g); Espectro NMR: ($CDCl_3$) 1.4 (d, 3H), 1.45 (s, 9H), 3.3 (m, 2H), 3.8 (m, 2H), 4.6 (m, 2H), 5.0 (q, 1H).

Una solución 5M enfriada de cloruro de hidrógeno en isopropanol (4 ml) se agregó a una solución de tert-butil (3RS,4SR)-3,4-etilidendioxipirrolidin-1-carboxilato (0.475 g) en cloruro de metileno (25 ml) que se enfrió en un baño de aceite. La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 2 horas. El disolvente se evaporó y el residuo se trituró bajo éter dietílico. El precipitado se recogió por filtración, se lavó con éter dietílico y se secó. Se obtuvo así clorhidrato de (3RS,4SR)-3,4-etilidendioxipirrolidina (0.28 g); Espectro NMR: ($DMSOd_6$ y CD_3CO_2D) 1.35 (d, 3H), 3.1 (d, 2H), 3.4 (d, 2H), 4.75 (s, 2H), 4.9 (q, 1H).

El material así obtenido se disolvió en cloruro de metileno y se agregó una solución 7M de amoníaco metanólico (0.2 ml). La mezcla resultante se agitó a temperatura ambiente durante 5 minutos. La mezcla se filtró y el disolvente se evaporó a temperatura ambiente bajo vacío. Se obtuvo así (3RS,4SR)-3,4-etilidendioxipirrolidina la cual se utilizó sin ninguna purificación adicional.

[30] Los reactivos fueron 7-(2-cloroetoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino) quinazolina y 1-metilpiperazina. El producto requerido así obtenido en 74% de rendimiento produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$ y CD_3CO_2D) Espectro de Masa: $M+H^+$ 501 y 503; Análisis Elemental: Hallado C, 57.5; H, 6.5; N, 16.0; $C_{24}H_{29}ClN_6O_4$ $0.23H_2O$ requiere C, 57.8; H, 6.1; N, 16.2%.

[31] Los reactivos fueron 7-(3-cloropropoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxiquinazolina (cuya preparación se

172

describe en Ejemplo 12 más adelante) y morfolina. El producto requerido así obtenido en 39% de rendimiento produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$) 1.55 (d, 6H), 2.05 (m, 2H), 2.45 (m, 4H), 2.55 (t, 2H), 3.7 (m, 4H), 4.15 (t, 2H), 4.85 (m, 1H), 6.15 (s, 2H), 6.5 (s,1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Espectro de Masa: $M+H^+$ 502 y 504; Análisis Elemental: Hallado C, 57.3; H, 5.65; N, 13.6; $C_{24}H_{28}ClN_5O_5$ requiere C, 57.4; H, 5.6; N, 13.95%.

[32] Los reactivos fueron 7-(3-cloropropoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)quinazolina (cuya preparación se describe en Ejemplo 13 más adelante) y morfolina. El producto requerido así obtenido en 45% de rendimiento produjo los siguientes datos característicos; Espectro NMR: ($DMSOd_6$ y CF_3CO_2D) 2.3 (m, 2H), 3.15 (m, 2H), 3.35 (m, 2H), 3.5 (m, 2H), 3.7 (m, 2H), 4.05 (m, 2H), 4.35 (m, 2H), 6.3 (s, 2H), 7.35 (s, 1H), 7.6 (d, 1H), 7.9 (s, 1H), 8.7 (d, 1H), 9.05 (s, 1H); Espectro de Masa: $M+H^+$ 444 y 446; Análisis Elemental: Hallado C, 57.0; H, 5.1; N, 15.7; $C_{21}H_{22}ClN_5O_4$ requiere C, 56.8; H, 5.0; N, 15.8%.

[33] Los reactivos fueron 7-(3-cloropropoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino) quinazolina y 1-acetilpiperazin. El producto requerido así obtenido en 34% de rendimiento produjo los siguientes datos característicos; Espectro NMR: ($DMSOd_6$ y CF_3CO_2D) 2.05 (s, 3H), 2.3 (s, 2H), 3.0 (m, 2H), 3.15 (m, 1H), 3.3-3.4 (m, 4H), 3.6 (m, 2H), 4.05 (m, 1H), 4.35 (m, 2H), 4.5 (m, 1H), 6.3 (s, 2H), 7.35 (s, 1H), 7.6 (d, 1H), 7.9 (s, 1H), 8.7 (d, 1H), 9.0 (s, 1H); Espectro de Masa: $M+H^+$ 485 y 487; Análisis Elemental: Hallado C, 56.9; H, 5.4; N, 16.6; $C_{23}H_{25}ClN_6O_4$ $0.15Et_2O$ requiere C, 57.1; H, 5.4; N, 16.9%.

[34] Los reactivos fueron 7-(2-cloroetoxi)-4-(2,3-metilendioxipirid-4-ilamino)quinazolina (cuya preparación se describe en Ejemplo 14 más adelante) y 1-prop-2-inilpiperazina. Luego de enfriar la mezcla de reacción y evaporar el disolvente, el residuo se trituró bajo agua y el precipitado resultante se aisló, se lavó con agua y éter dietílico y se secó. El producto requerido así obtenido en 60% de rendimiento produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$) 2.26 (s, 1H), 2.8-2.6 (m, 8H), 2.97

(t, 2H), 3.3 (s, 2H); 4.03 (s, 3H), 4.33 (t, 2H), 6.14 (s, 2H), 6.98 (s, 1H), 7.12 (br s, 1H), 7.30 (s, 1H), 7.73 (d, 1H), 8.08 (d, 1H), 8.76 (s, 1H); Espectro de Masa: $M+H^+$ 463.

[35] Los reactivos fueron 7-(3-cloropropoxi)-4-(2,3-metilendioxipirid-4-ilamino)quinazolina (cuya preparación se describe en Ejemplo 15 más adelante) y 1-prop-2-inilpiperazina. El producto requerido así obtenido en 57% de rendimiento produjo los siguientes datos característicos; Espectro NMR: ($CDCl_3$) 2.13 (m, 2H), 2.26 (s, 1H), 2.6 (m, 10H), 3.31 (s, 2H), 4.04 (s, 3H), 4.26 (t, 2H), 6.14 (s, 2H), 6.98 (s, 1H), 7.12 (br s, 1H), 7.31 (s, 1H), 7.72 (d, 1H), 8.08 (d, 1H), 8.76 (s, 1H); Espectro de Masa: $M+H^+$ 477.

Ejemplo 7

6-(2-cloroetoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-metoxiquinazolina

Usando un procedimiento análogo al descrito en Ejemplo 1, 4-cloro-6-(2-cloroetoxi)-7-metoxiquinazolina se hizo reaccionar con 4-amino-5-cloro-2,3-metilendioxipiridina para producir el compuesto del título en 59% de rendimiento; Espectro NMR: ($CDCl_3$) 3.95 (t, 2H), 4.05 (s, 3H), 4.4 (t, 2H), 6.1 (s, 2H), 7.05 (s, 1H), 7.2 (s, 1H), 7.35 (s, 1H), 7.75 (s, 1H), 8.75 (s, 1H); Espectro de Masa: $M+H^+$ 409 y 411.

La 4-cloro-6-(2-cloroetoxi)-7-metoxiquinazolina usada como material de partida se preparó como sigue:-

Una mezcla de 6-acetoxi-7-metoxi-3,4-dihidroquinazolin-4-ona (Solicitud Internacional de Patente WO 96/15118, Ejemplo 39 de la misma; 8 g), cloruro de tionilo (80 ml) y DMF (0.8 ml) se agitó y se calentó a 80°C durante 1.5 horas. La mezcla se enfrió a temperatura ambiente y el cloruro de tionilo se evaporó. El material así obtenido se suspendió en tolueno y se evaporó a sequedad (dos veces). El residuo resultante se diluyó con cloruro de metileno (5 ml) y una mezcla 10:1 (290 ml) de metanol y se agregó una solución de hidróxido de amonio acuoso saturado. La mezcla resultante se agitó y se calentó a 80°C durante 5 minutos. El disolvente se evaporó y el residuo sólido se suspendió en agua. Se ajustó la alcalinidad de la mezcla a

pH 7 por la adición de solución de ácido clorhídrico acuoso diluído. El sólido resultante se recogió por filtración, se lavó con agua y se secó bajo vacío sobre pentóxido de fósforo. Se obtuvo así 4-cloro-6-hidroxi-7-metoxiquinazolina (6.08 g) la cual se usó sin más purificación; Espectro NMR: ($DMSOd_6$) 4.05 (s, 3H), 7.4 (s, 1H), 7.45 (s, 1H), 8.8 (s, 1H).

Di-tert-butil azodicarboxilato (1.53 ml) se agregó en porciones durante unos pocos minutos a una mezcla agitada de 4-cloro-6-hidroxi-7-metoxiquinazolina (1 g), 2-cloroetanol (0.382 ml), trifenilfosfamida (1.74 g) y cloruro de metileno (30 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. La mezcla se evaporó y el residuo se purificó por cromatografía de columna en sílice usando mezclas crecientemente polares de cloruro de metileno y acetato de etilo como eluyente. Se obtuvo así 4-cloro-6-(2-cloroetoxi)-7-metoxiquinazolina como un sólido blanco (1.06 g); Espectro NMR: ($CDCl_3$) 3.95 (t, 2H), 4.05 (s, 3H), 4.45 (t, 2H), 7.35 (s, 1H), 7.4 (s, 1H), 8.9 (s, 1H).

Ejemplo 8

6-(3-cloropropoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-metoxiquinazolina

Usando un procedimiento análogo al descrito en Ejemplo 1, 4-cloro-6-(3-cloropropoxi)-7-metoxiquinazolina se hizo reaccionar con 4-amino-5-cloro-2,3-metilendioxipiridina para producir el compuesto del título en 58% de rendimiento; Espectro NMR: ($CDCl_3$) 2.4 (m, 2H), 3.8 (t, 2H), 4.05 (s, 3H), 4.35 (t, 2H), 6.15 (s,2H), 7.05 (s, 1H), 7.2 (s, 1H), 7.3 (s, 1H), 7.75 (s, 1H), 8.7 (s, 1H); Espectro de Masa: $M+H^+$ 423 y 425.

La 4-cloro-6-(3-cloropropoxi)-7-metoxiquinazolina usada como material de partida se preparó como sigue:-

Di-tert-butil azodicarboxilato (1.84 g) se agregó en porciones durante uno cuantos minutos a una mezcla agitada de 4-cloro-6-hidroxi-7-metoxiquinazolina (1.2 g), 3-cloropropanol (0.572 ml), trifenilfosfamida (2.1 g) y cloruro de metileno (30 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 3 horas. La mezcla se evaporó y el residuo se

purificó por cromatografía de columna en sílice usando mezclas crecientemente polares de cloruro de metileno y acetato de etilo como eluyente. El material así obtenido se trituró bajo éter dietílico. El sólido resultante se aisló y se secó bajo vacío. Se obtuvo así 4-cloro-6-(3-cloropropoxi)-7-metoxiquinazolina como un sólido blanco (0.84 g); Espectro NMR: ($CDCl_3$) 2.4 (m, 2H), 3.8 (t, 2H), 4.05 (s, 3H), 4.35 (t, 2H), 7.35 (s, 1H), 7.45 (s, 1H), 8.9 (s, 1H).

Ejemplo 9

4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(3-cloropropoxi)-5-tetrahidropiran-4-iloxiquinazolina

Usando un procedimiento análogo al descrito en Ejemplo 1, 4-cloro-7-(3-cloropropoxi)-5-tetrahidropiran-4-iloxiquinazolina se hizo reaccionar con 4-amino-5-cloro-2,3-metilendioxipiridina para producir el compuesto del título en 78% de rendimiento; Espectro de Masa: $M+H^+$ 493 y 495.

La 4-cloro-7-(3-cloropropoxi)-5-tetrahidropiran-4-iloxiquinazolina usada como material de partida se preparó como sigue:-

Usando un procedimiento análogo al descrito en la porción de Ejemplo 4 que atañe a la preparación de materiales de partida, 4-cloro-7-hidroxi-5-tetrahidropiran-4-iloxiquinazolina (2.5 g) se hizo reaccionar con 3-cloropropanol. Se obtuvo así el material de partida requerido 21% de rendimiento; Espectro NMR: ($DMSOd_6$ y CF_3CO_2D) 1.7 (m, 2H), 2.0 (m, 2H), 2.25 (m, 2H), 3.55 (m, 2H), 3.8 (t, 2H), 3.9 (m, 2H), 4.3 (t, 2H), 4.95 (m, 1H), 6.8 (s, 1H), 6.9 (s, 1H), 9.2 (s, 1H).

Ejemplo 10

4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(2,4-dimetoxibenciloxi)-5-isopropoxiquinazolina

Usando un procedimiento análogo al descrito en Ejemplo 1, 4-cloro-7-(2,4-dimetoxibenciloxi)-5-isopropoxiquinazolina se hizo reaccionar con 4-amino-5-cloro-2,3-metilendioxipiridina para producir el compuesto del título en 75% de rendimiento; Espectro NMR: ($CDCl_3$) 1.55 (d, 6H), 3.8 (s,

3H), 3.85 (s, 3H), 4.8 (m, 1H), 5.15 (s, 2H), 6.15 (s, 2H), 6.5 (m, 2H), 6.6 (s, 1H), 7.0 (s, 1H), 7.35 (d, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Espectro de Masa: $M+H^+$ 525 y 527.

La 4-cloro-7-(2,4-dimetoxibenciloxi)-5-isopropoxiquinazolina usada como material de partida se preparó como sigue:-

Hidruro de sodio (dispersión del 60% en aceite mineral; 40 g) se agregó en porciones a una solución de isopropanol (30 g) en DMF (500 ml) que se había enfriado a 5°C. La mezcla se dejó calentar a temperatura ambiente y se agitó durante 60 minutos. Se agregó 5,7-difluoro-3,4-dihidroquinazolin-4-ona (Solicitud Internacional de Patente WO 01/94341; 90 g) y la mezcla se agitó a temperatura ambiente durante 3 horas. La mezcla se vertió en agua (1 litro) y, con agitación vigorosa, se agregó ácido acético glacial para acidificar la mezcla a pH 5. El sólido resultante se aisló, se lavó con agua y con éter dietílico y se secó bajo vacío. Se obtuvo así 7-fluoro-5-isopropoxi-3,4-dihidroquinazolin-4-ona (79 g); Espectro NMR: ($DMSOd_6$) 1.31 (s, 6H), 4.73 (m, 1H), 6.89 (m, 1H), 6.95 (m, 1H), 7.96 (s, 1H); Espectro de Masa: $M+H^+$ 223.

Una mezcla de 7-fluoro-5-isopropoxi-3,4-dihidroquinazolin-4-ona (61 g), alcohol 2,4-dimetoxibencílico (138 g), tert-butóxido de potasio (185 g) y THF (1.5 litros) se agitó y se calentó a reflujo durante 18 horas. Luego de enfriar, el disolvente se evaporó y se agregó una mezcla de cloruro de metileno (400 ml) y agua (600 ml). Con el enfriamiento, la mezcla de 2 fases se neutralizó por la adición de 2N de ácido clorhídrico acuoso. La mezcla se filtró y la fase orgánica se separó, se secó sobre sulfato de magnesio y se evaporó. El residuo se trituró bajo éter dietílico. Se obtuvo así 7-(2,4-dimetoxibenciloxi)-5-isopropoxi-3,4-dihidroquinazolin-4-ona (68 g); Espectro NMR: ($DMSOd_6$) 1.28 (s, 6H), 3.78 (s, 3H), 3.82 (s, 3H), 4.63 (m, 1H), 5.06 (s, 2H), 6.55 (m, 2H), 6.62 (s, 1H), 6.71 (s, 1H), 7.33 (d, 1H), 7.88 (s, 1H); Espectro de Masa: $M+H^+$ 371.

Una mezcla de una porción (4 g) del material así obtenido, oxicloruro de fósforo (1.98 g), diisopropiletilamina (3.6 g) y cloruro de metileno (100 ml) se agitó y se calentó a 75°C durante 3 horas. La mezcla se enfrió y se

evaporó. El residuo se secó bajo vacío durante 1 hora y se purificó por cromatografía de columna en sílice usando una mezcla 20:3 de cloruro de metileno y acetato de etilo como eluyente. Se obtuvo así 4-cloro-7-(2,4-dimetoxibenciloxi)-5isopropoxiquinazolina como un sólido (2.63 g); Espectro NMR: ($CDCl_3$) 1.46 (s, 3H), 1.47 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 4.68 (m, 1H), 5.16 (s, 2H), 6.52 (m, 2H), 6.65 (s, 1H), 7.06 (s, 1H), 7.33 (d, 1H), 8.78 (s, 1H); Espectro de Masa: $M+H^+$ 389.

Ejemplo 11

4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-hidroxi-5-isopropoxiquinazolina

Ácido trifluoroacético (4.5ml) se agregó a una solución de 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(2,4-dimetoxibenciloxi)-5-isopropoxiquinazolina (0.53 g) en cloruro de metileno (9 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 30 minutos. Los disolventes se evaporaron para producir la sal del ácido di-trifluoroacético (0.618 g) del compuesto requerido. Una porción de esta sal se disolvió en cloruro de metileno (2 ml) y se agregó una solución 7M de amoníaco metanólico. La mezcla se filtró y el filtrado se evaporó. Se obtuvo así el compuesto del título; Espectro de Masa: $M+H^+$ 375 y 377.

Ejemplo 12

4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(3-cloropropoxi)-5-isopropoxiquinazolina

Una mezcla de sal de ácido 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-hidroxi-5-isopropoxiquinazolin-ditrifluoroacético (0.615 g), 1,3-dicloropropano (0.38 ml), carbonato de potasio (0.56 g) y DMF (6 ml) se agitó y se calentó a 80°C durante 5 horas. Luego de enfriar, los sólidos se extrajeron por filtración y el filtrado se evaporó. El residuo se purificó por cromatografía de columna en sílice usando una mezcla 24:1 de cloruro de metileno y metanol como eluyente. Se obtuvo así el compuesto del título (0.32 g); Espectro NMR: ($CDCl_3$) 1.55 (d, 6H), 2.3 (m, 2H), 3.8 (t, 2H),

4.25 (t, 2H), 4.9 (m, 1H), 6.15 (s, 2H), 6.5 (s, 1H), 6.9 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H).

Ejemplo 13

4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(3-cloropropoxi) quinazolina

Usando un procedimiento análogo al descrito en Ejemplo 1, 4-cloro-7-(3-cloropropoxi)quinazolina se hizo reaccionar con 4-amino-5-cloro-2,3-metilendioxipiridina para producir el compuesto del título en 89% de rendimiento; Espectro NMR: ($DMSOd_6$ y CF_3CO_2D) 2.25 (m, 2H), 3.8 (t, 2H), 4.35 (t, 2H), 6.25 (s, 2H), 7.35 (s, 1H), 7.6 (d, 1H), 7.9 (s, 1H), 8.7 (d, 1H), 9.0 (s, 1H).

La 4-cloro-7-(3-cloropropoxi)quinazolina usada como material de partida se preparó como sigue:-

Hidruro de sodio (dispersión del 60% en aceite mineral; 2.92 g) se agregó en porciones durante 45 minutos a una mezcla agitada de 1,3-propanodiol (5.3 ml) y DMF (20 ml) que se había enfriado a 0°C. La mezcla resultante se agitó a temperatura ambiente durante 1 hora y luego se calentó a 60°C. Se agregó 7-fluoro-3,4-dihidroquinazolin-4-ona (Solicitud Internacional de Patente WO 01/04102, Ejemplo 2, Nota [12] de la misma; 2 g) y la mezcla de reacción se agitó y se calentó a 115°C durante 3.5 horas. La mezcla de reacción se enfrió a 0°C y se agregó agua (50 ml). La mezcla se acidificó a pH 5.9 con 2N de ácido clorhídrico. El precipitado resultante se recogió por filtración, se lavó con aguay se secó bajo vacío sobre pentóxido de fósforo a 40°C. El sólido así obtenido se lavó con éter dietílico y se secó nuevamente bajo vacío. Se obtuvo así 7-(3-hidroxipropoxi)-3,4-dihidroquinazolin-4-ona (2.1 g); Espectro NMR: ($DMSOd_6$) 1.9 (m, 2H), 3.6 (m, 2H), 4.15 (m, 2H), 4.6 (br s, 2H), 7.1 (m, 2H), 8.05 (m, 2H); Espectro de Masa: $M+H^+$ 221.

Una mezcla de 7-(3-hidroxipropoxi)-3,4-dihidroquinazolin-4-ona (1 g), 1,2-dicloroetano (50 ml), trifenilfosfamida (5.24 g) y tetracloruro de carbono (2.9 ml) se agitó y se calentó a 70°C durante 2 horas. El disolvente

se evaporó y el residuo se purificó por cromatografía de columna en sílice usando inicialmente cloruro de metileno seguido por un incremento gradual de la polaridad del disolvente hasta una mezcla 9:1 de cloruro de metileno y metanol como eluyente. Se obtuvo así 4-cloro-7-(3-cloropropoxi) quinazolina (1.23 g; que contenía 0.6 moles de óxido de trifenilfosfamida por mol de producto); Espectro de Masa: $M+H^+$ 393 y 395.

Ejemplo 14

7-(2-cloroetoxi)-4-(2,3-metilendioxipirid-4-ilamino)-6-metoxiquinazolina

Hexametildisilazano de sodio (solución 1M en THF; 2 ml) se agregó gota a gota a una mezcla de 4-amino-2,3-metilendioxipiridina (0.138 g), 4-cloro-7-(2-cloroetoxi)-6-metoxiquinazolina (0.272 g) y THF (5 ml) que se había enfriado a 0°C. La mezcla se agitó a 0°C durante 1 hora. La mezcla resultante se dejó calentar a temperatura ambiente y se agitó durante 2 horas. La reacción se atemperó por la adición de ácido acético glacial (0.12 ml). Los disolventes se evaporaron y el residuo se dividió en porciones entre cloruro de metileno y una solución de hidróxido de amonio acuoso. La capa orgánica se recogió y se concentró en un volumen pequeño. Se agregó éter dietílico y se formó un precipitado. El sólido resultante se aisló, se lavó con éter dietílico y se secó. Se obtuvo así el compuesto del título (0.245 g); Espectro NMR: ($DMSOd_6$) 3.97 (s, 3H), 4.04 (m, 2H), 4.45 (m, 2H), 6.12 (s, 2H), 7.13 (br d, 1H), 7.25 (s,1H), 7.60 (d, 1H), 7.83 (s, 1H), 8.47 (s, 1H), 9.87 (br s, 1H); Espectro de Masa: $M+H^+$ 375.

La 4-amino-2,3-metilendioxipiridina usada como material de partida se preparó como sigue:-

Dibromometano (31.5 ml) se agregó a una mezcla de 2,3-dihidroxipiridina (33 g), carbonato de potasio (62 g) y NMP (200 ml) y la mezcla se agitó y se calentó a 90°C durante 16 horas. La mezcla se enfrió a temperatura ambiente y se filtró. El filtrado se dividió en porciones entre éter dietílico (5 x 100 ml) y agua (200 ml). Los extractos orgánicos se combinaron y se concentraron bajo vacío en un volumen aproximado de 20

ml. Se agregó éter de petróleo (b.p. 40-60°C; 300 ml) y la solución se lavó con salmuera. La capa orgánica se separó y se evaporó. Se obtuvo así 2,3-metilendioxipiridina como un líquido (5.1 g); Espectro NMR: ($CDCl_3$) 6.05 (s, 2H), 6.76 (m, 1H), 6.99 (d, 1H), 7.65 (d, 1H).

Usando un procedimiento análogo al descrito en el segundo párrafo de la porción de Ejemplo 1, que atañe a la preparación del material de partida, 4-amino-5-cloro-2,3-metilendioxipiridina, 2,3-metilendioxipiridina se hizo reaccionar con gas de dióxido de carbono para producir ácido 2,3-metilendioxipiridin-4-carboxílico en 80% de rendimiento; Espectro NMR: ($DMSOd_6$) 6.24 (s, 2H), 7.13 (d, 1H); 7.63 (d, 1H).

Usando un procedimiento análogo al descrito en el tercer párrafo de la porción de Ejemplo 1 que atañe a la preparación de materiales de partida, ácido 2,3-metilendioxipiridin-4-carboxílico se hizo reaccionar con azida de difenilfosforilo y tert-butanol anhidro para producir tert-butil 2,3-metilendioxipirid-4-ilcarbamato en 62% de rendimiento; Espectro de Masa: $M+H^+$ 239.

Usando un procedimiento análogo al descrito en el último párrafo de la porción de Ejemplo 1 que atañe a la preparación de materiales de partida, tert-butil 2,3-metilendioxipirid-4-ilcarbamato se hizo reaccionar con ácido trifluoroacético para producir 4-amino-2,3-metilendioxipiridina en 80% de rendimiento; Espectro NMR: ($CDCl_3$) 3.98 (m, 2H), 5.98 (s, 2H), 6.24 (d, 1H), 7.44 (d, 1H); Espectro de Masa: $M+H^+$ 139.

Ejemplo 15

7-(3-cloropropoxi)-4-(2,3-metilendioxipirid-4-ilamino)-6-metoxiquinazolina

Usando un procedimiento análogo al descrito en Ejemplo 14, 4-cloro-7-(3-cloropropoxi)-6-metoxiquinazolina se hizo reaccionar con 4-amino-2,3-metilendioxipiridina para producir el compuesto del título en 68% de rendimiento; Espectro NMR: ($DMSOd_6$) 2.26 (m, 2H), 3.83 (m, 2H), 3.96 (s, 3H), 4.28 (m, 2H), 6.12 (s, 2H), 7.15 (br d, 1H), 7.25 (s, 1H), 7.61 (d, 1H), 7.81 (s, 1H), 8.49 (s, 1H), 9.79 (br s, 1H); Espectro de Masa: $M+H^+$

181

389.

Ejemplo 16

7-[2-(4-acetilpiperazin-1-il)etoxi]-4-(2,3-metilendioxipirid-4-ilamino)-5-tetrahidropiran-4-iloxiquinazolina

Usando un procedimiento análogo al descrito en Ejemplo 1, 7-[2- (4-acetilpiperazin-1-il)etoxi]-4-cloro-5-tetrahidropiran-4-iloxiquinazolina (0.113 g) se hizo reaccionar con 4-amino-2,3-metilendioxipiridina (0.036 g). La mezcla de reacción se atemperó con ácido acético glacial (0.031 g) y se diluyó con metanol. La mezcla se evaporó y el residuo se purificó por cromatografía de columna en una columna de sílice de fase reversa C18 (columna Waters Symmetry, sílice de 5 micrones, 20 mm diámetro, 100 mm longitud) usando una mezcla decrecientemente polar de agua y acetonitrilo (que contenía ácido acético al 1%) como eluyente. El material así obtenido se diluyó con una solución 7M de amoníaco metanólico. La mezcla se evaporó y el material así obtenido se disolvió en cloruro de metileno. La solución se secó sobre sulfato de magnesio y se evaporó para producir el compuesto del título como una espuma en 53% de rendimiento; Espectro NMR: ($CDCl_3$) 2.02 (m, 2H), 2.1 (s, 3H), 2.22 (m, 2H), 2.6 (m,4H), 2.9 (m, 2H), 3.51 (m, 2H), 3.6 (m, 2H), 3.66 (m, 2H), 4.1 (m, 2H), 4.25 (m, 2H), 4.73 (m, 1H), 6.13 (s, 2H), 6.59 (s, 1H), 6.9 (s, 1H), 7.7 (d, 1H), 8.36 (d, 1H), 8.66 (s, 1H); Espectro de Masa: $M+H^+$ 537.

La 7-[2-(4-acetilpiperazin-1-il)etoxi]-4-cloro-5-tetrahidropiran-4-iloxiquinazolina usada como material de partida se preparó como sigue:-

Hidruro de sodio (dispersión del 60% en aceite mineral; 0.6 g) se agregó en porciones a una solución de 4-hidroxitetrahidropirano (0.78 g) en DMF (10 ml) que se había enfriado a 5°C. La mezcla se dejó calentar a temperatura ambiente y se agitó durante 15 minutos. Se agregó 5,7-difluoro-3,4-dihidroquinazolin-4-ona (Solicitud Internacional de Patente WO 01/94341; 0.9 g) y la mezcla se agitó a temperatura ambiente durante 30 minutos. La mezcla se vertió en agua (100 ml) y, con agitación vigorosa, se agregó ácido acético glacial para acidificar la mezcla a pH 5.

182

El sólido resultante se aisló, se lavó con agua y con éter dietílico y se secó bajo vacío. Se obtuvo así 7-fluoro-5-tetrahidropiran-4-iloxi-3,4-dihidroquinazolin-4-ona (1.1 g); Espectro NMR: ($DMSOd_6$) 1.6-1.75 (m, 2H), 1.9-2.0 (m, 2H), 3.5-3.6 (m, 2H), 3.85-3.95 (m, 2H), 4.8 (m, 1H), 6.9 (m, 1H), 7.05 (m, 1H), 8.0 (s, 1H); Espectro de Masa: $M+H^+$ 265.

Luego de la repetición de la anterior reacción, una mezcla de 7-fluoro-5-tetrahidropiran-4-iloxi-3,4-dihidroquinazolin-4-ona (5.3 g), 2-piperazin-1-iletanol (3.9 g), tert-butóxido de potasio (6.7 g) y THF (200 ml) se agitó y se calentó a reflujo durante 3 horas. Se agregó una segunda porción (6.7 g) de tert-butóxido de potasio y la mezcla se calentó reflujo durante 12 horas más. La mezcla se enfrió a temperatura ambiente y se filtró. El filtrado se evaporó y el residuo se purificó por cromatografía de columna en sílice usando mezclas crecientemente polares de cloruro de metileno y una solución 7M de amoníaco metanólico como eluyente. El material así obtenido se trituró bajo éter dietílico. Se obtuvo así 7-(2-piperazin-1-iletoxi)-5-tetrahidropiran-4-iloxi-3,4-dihidroquinazolin-4-ona (5.2 g); Espectro NMR: ($DMSOd_6$ y CF_3CO_2D) 1.75 (m, 2H), 2.03 (m, 2H), 3.2-4.0 (m, 14H), 4.59 (m, 2H), 4.92 (m, 1H), 6.88 (s, 1H), 6.9 (s, 1H), 9.28 (s, 1H); Espectro de Masa: $M+H^+$ 375.

Anhídrido acético (1.51 ml) se agregó gota a gota a una mezcla agitada de 7-(2-piperazin-1-iletoxi)-5-tetrahidropiran-4-iloxi-3,4-dihidroquinazolin-4-ona (5 g) y agua (20 ml) y la mezcla resultante se agitó a temperatura ambiente durante 10 minutos. La mezcla de reacción se evaporó y el residuo se trituró bajo éter dietílico. El sólido resultante se aisló, se lavó con éter dietílico y se secó bajo vacío. Se obtuvo así 7-[2-(4-acetilpiperazin-1-il)etoxi]-5-tetrahidropiran-4-iloxi-3,4-dihidroquinazolin-4-ona (5.5 g); Espectro NMR: ($DMSOd_6$ y CF_3CO_2D) 1.75 (m, 2H), 2.03 (m, 2H), 2.08 (s, 3H), 3.0-4.2 (m, 13H), 4.56 (m, 3H), 4.94 (m, 1H), 6.84 (s, 1H), 6.9 (s, 1H), 9.21 (s, 1H); Espectro de Masa: $M+H^+$ 417.

Una mezcla de una porción (0.416 g) del material así obtenido, trifenilfosfamida (0.655 g), tetracloruro de carbono (0.34 ml) y 1,2-dicloroetano (20 ml) se agitó y se calentó a 70°C durante 1.5 horas. La

183

mezcla se evaporó y el residuo se purificó por cromatografía de columna en sílice usando mezclas crecientemente polares de cloruro de metileno y una solución 7M de amoníaco metanólico (una gradiente de disolvente con solución de amoníaco metanólico de 1% a 3%) como eluyente. Se obtuvo así 7-[2-(4-acetilpiperazin-1-il)etoxi]-4-cloro-5-tetrahidropiran-4-iloxiquinazolina como un sólido (0.35 g); Espectro NMR: ($CDCl_3$) 2.0 (m, 2H), 2.1 (s, 3H), 2.12 (m, 2H), 2.58 (m, 4H), 2.9 (m, 2H), 3.51 (m, 2H), 3.68 (m, 4H), 4.05 (m, 2H), 4.25 (m, 2H), 4.75 (m, 1H), 6.62 (s, 1H), 6.94 (s, 1H), 8.82 (s, 1H); Espectro de Masa: $M+H^+$ 435 y 437.

Ejemplo 17

7-[2-(4-acetilpiperazin-1-il)etoxi]-4-(2,3-metilendioxipirid-4-ilamino)-5-isopropoxiquinazolina

Usando un procedimiento análogo al descrito en Ejemplo 16, 7-[2-(4-acetilpiperazin-1-il)etoxi]-4-cloro-5-isopropoxiquinazolina se hizo reaccionar con 4-amino-2,3-metilendioxipiridina para producir el compuesto del título en 55% de rendimiento; Espectro NMR: ($CDCl_3$) 1.55 (s, 3H), 1.56 (s, 3H), 2.1 (s, 3H), 2.59 (m, 4H), 2.89 (m, 2H), 3.51 (m, 2H), 3.67 (m, 2H), 4.24 (m, 2H), 4.85 (m, 1H), 6.13 (s, 2H), 6.57 (s, 1H), 6.85 (s, 1H), 7.71 (d, 1H), 8.41 (d, 1H), 8.66 (s, 1H); Espectro de Masa: $M+H^+$ 495.

La 7-[2-(4-acetilpiperazin-1-il)etoxi]-4-cloro-5-isopropoxiquinazolina que se requiere como material de partida se preparó como sigue usando procedimientos análogos a los descritos en la porción de Ejemplo 16 que atañe a la preparación de materiales de partida.

5,7-Difluoro-3,4-dihidroquinazolin-4-ona se hizo reaccionar con isopropanol para producir 7-fluoro-5-isopropoxi-3,4-dihidroquinazolin-4-ona en 73% de rendimiento; Espectro NMR: ($DMSOd_6$) 1.31 (s, 6H), 4.73 (m, 1H), 6.89 (m, 1H), 6.95 (m, 1H), 7.96 (s, 1H); Espectro de Masa: $M+H^+$ 223.

El material así obtenido se hizo reaccionar con 2-piperazin-1-iletanol para producir 5-isopropoxi-7-(2-piperazin-1-iletoxi)-3,4-dihidroquinazolin-4-ona en 63% de rendimiento; Espectro NMR: ($CDCl_3$) 1.45 (s, 3H), 1.46

184

(s, 3H), 2.4-3.0 (m, 10H), 4.2 (t, 2H), 4.62 (m, 1H), 6.51 (s, 1H), 6.72 (s, 1H), 7.9 (s, 1H).

El material así obtenido se hizo reaccionar con un exceso de anhídrido acético, pero usando cloruro de metileno en lugar de agua como el disolvente de reacción. La mezcla de reacción se agitó a temperatura ambiente durante 15 minutos. La mezcla se dividió en porciones entre cloruro de metileno y una solución de bicarbonato de sodio acuoso saturado. La capa orgánica se lavó con agua y con salmuera, se secó sobre sulfato de magnesio y se evaporó. El residuo se trituró bajo una mezcla de acetonitrilo y éter dietílico. Se obtuvo así 7-[2-(4-acetilpiperazin-1-il) etoxi]-5-isopropoxi-3,4-dihidroquinazolin-4-ona en 70% de rendimiento; Espectro NMR: ($CDCl_3$) 1.46 (s, 3H), 1.47 (s, 3H), 2.1 (s, 3H), 2.58 (m, 4H), 2.87 (t, 2H), 3.5 (m, 2H), 3.66 (m, 2H), 4.21 (t, 2H), 4.63 (m, 1H), 6.51 (s, 1H), 6.72 (s, 1H), 7.9 (s, 1H), 9.9 (br s, 1H); Espectro de Masa: $M+H^+$ 375.

El material así obtenido se hizo reaccionar con tetracloruro de carbono y trifenilfosfamida para producir 7-[2-(4-acetilpiperazin-1-il) etoxi]-4-cloro-5-isopropoxiquinazolina en 68% de rendimiento, la cual se usó sin más purificación.

Ejemplo 18

4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-{2-[4-(2-dimetilaminoacetil)piperazin-1-il]etoxi}-5-isopropoxiquinazolina

4-(5-Cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxi-7-(2-piperazin-1-iletoxi)quinazolina (0.2 g) se agregó a una mezcla agitada de clorhidrato de 2-dimetilaminoacetil cloruro (0.097 g), trietilamina (0.15 ml) y cloruro de metileno (5 ml) que se había enfriado a 0°C. La mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 2 horas. Se agregó una segunda porción de cada uno de clorhidrato de 2-dimetilaminoacetil cloruro (0.097 g) y trietilamina (0.057 ml) y la reacción se agitó a temperatura ambiente durante 16 horas de un día para otro. Se agregó cloruro de metileno (50 ml) y la mezcla de reacción se extrajo dos

185

veces con una solución de bicarbonato de sodio acuoso saturado. La fase orgánica se secó sobre sulfato de magnesio y se evaporó. El residuo se purificó por cromatografía de columna en sílice usando mezclas de disolvente crecientemente polares, comenzando con una mezcla 9:1 de cloruro de metileno y metanol y finalizando con una mezcla 90:8:2 de cloruro de metileno, metanol y una solución de amoníaco metanólico saturado. Se obtuvo así el compuesto del título como una espuma (0.155 g); Espectro NMR: ($CDCl_3$) 1.55 (d, 6H), 2.3 (s, 6H), 2.6 (m, 4H), 2.9 (t, 2H), 3.1 (s, 2H), 3.65 (m, 4H), 4.25 (t, 2H), 4.85 (s, 1H), 6.15 (s, 2H), 6.55 (s, 1H), 6.85 (s, 1H), 7.75 (s, 1H), 8.6 (s, 1H), 9.6 (s, 1H); Espectro de Masa: $M+H^+$ 572 y 574; Análisis Elemental: Hallado C, 55.1; H, 6.1; N, 16.8; $C_{27}H_{34}ClN_7O_5$ $0.75H_2O$ requiere C, 55.4; H, 6.1; N, 16.7%.

Ejemplo 19

7-(N-tert-butoxicarbonilpiperidin-4-ilmetoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-metoxiquinazolina

Usando un procedimiento similar al descrito en Ejemplo 1, una solución de 4-amino-5-cloro-2,3-metilendioxipiridina (0.193 g) en DMF (2 ml) se agregó a una suspensión agitada de hidruro de sodio (dispersión del 60% en aceite mineral, 0.048 g) en DMF (2 ml) y la mezcla se agitó a temperatura ambiente durante 15 minutos. Se agregó una solución de 7-(N-tert-butoxicarbonilpiperidin-4-ilmetoxi)-4-cloro-6-metoxiquinazolina [Solicitud Internacional de Patente WO 02/16352 (Nota [24] en Ejemplo 2 de la misma; 0.38 g] en DMF (4 ml) y la mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se dividió en porciones entre acetato de etilo y salmuera. La fase orgánica se secó sobre sulfato de magnesio y se evaporó. El residuo se purificó por cromatografía de columna en sílice usando una mezcla 49:1 de cloruro de metileno y metanol. Se obtuvo así el compuesto del título como un sólido (0.24g); Espectro NMR: ($DMSOd_6$) 1.29 (m, 2H), 1.45 (s, 9H), 1.8 (m, 2H), 2.04 (m, 1H), 2.83 (m, 2H), 4.0 (m, 7H), 8.12 (br s, 2H), 7.17 (br s, 1H), 7.72 (m, 2H), 8.37 (br s, 1H), 9.37 (br s, 1H); Espectro de Masa: $M+H^+$ 544 y

546.

Ejemplo 20

4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-metoxi-7-(piperidin-4-ilmetoxi)quinazolina

Ácido trifluoroacético (1 ml) se agregó a una solución de 7-(N-tert-butoxicarbonilpiperidin-4-ilmetoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-metoxiquinazolina (0.253 g) en cloruro de metileno (10 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se evaporó. Se agregó tolueno al residuo y la mezcla se evaporó. El residuo se purificó por cromatografía de columna en sílice (columna Isolute SCX) usando una solución 7M de amoníaco metanólico como eluyente. Se obtuvo así el compuesto del título como un sólido (0.187 g); Espectro NMR: ($DMSOd_6$) 1.25 (m, 2H), 1.75 (d, 2H), 1.93 (m, 1H), 2.54 (m, 2H), 3.0 (d, 2H), 3.93 (s, 3H), 3.98 (d, 2H), 6.17 (s, 2H), 7.15 (s, 1H), 7.76 (s, 1H), 7.78 (s, 1H), 8.23 (s, 1H); Espectro de Masa: $M+H^+$ 444 y 446.

Ejemplo 21

4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-[N-(2-dimetilaminoacetil)piperidin-4-ilmetoxi]-6-metoxiquinazolina

Diisopropiletilamina (0.118 ml) se agregó a una mezcla de 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-metoxi-7-(piperidin-4-ilmetoxi)quinazolina (0.15 g), N,N-dimetilglicina (0.042 g), hexafluorofosfato de 2-(7-azabenzotriazol-1-il)-1,1,3,3-tetrametiluronio (V) (0.154 g) y DMF (3 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 16 horas. La mezcla se diluyó con acetato de etilo y se lavó con salmuera. La solución orgánica se secó sobre sulfato de magnesio y se evaporó. El residuo se purificó por cromatografía de columna en sílice usando una mezcla 100:3 de cloruro de metileno y una solución 7M de amoníaco metanólico como eluyente. Se obtuvo así el compuesto del título como un sólido (0.051 g); Espectro NMR: ($DMSOd_6$) 1.11-1. 36 (m, 2H),

1.83 (d, 2H), 2.11 (m, 1H), 2.19 (s, 6H), 2.61 (t, 1H), 3.03 (m, 2H), 3.12 (d, 1H), 3.93 (s, 3H), 4.06 (m, 3H), 4.4 (d, 1H), 6.19 (br s, 2H), 7.19 (br s, 1H), 7.78 (m, 2H), 8.39 (br s, 1H), 9.71 (br s, 1H); Espectro de Masa: $M+H^+$ 529 y 531.

Ejemplo 22

7-[2-(4-acetilpiperazin-1-il)etoxi]-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxiquinazolina

Una mezcla de 7-(2-cloroetoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxiquinazolina (24 g), 1-acetilpiperazina (21 g), yoduro de potasio (18 g) y DMA (500 ml) se agitó y se calentó a 100°C durante 4 horas. El disolvente se evaporó y el residuo se dividió en porciones entre cloruro de metileno (1 litro) y agua (500 ml). La capa acuosa se extrajo con cloruro de metileno. Se combinaron las soluciones orgánicas, se lavaron con salmuera, se secaron sobre sulfato de magnesio y se evaporaron. El residuo se purificó por cromatografía de columna en sílice usando mezclas crecientemente polares de cloruro de metileno y metanol (de una mezcla 20:1 a una mezcla 10:1) como eluyente. Tras la evaporación del disolvente, el material así obtenido se trituró bajo éter dietílico. Se obtuvo así el compuesto del título como un sólido blanco (26.2 g); m.p. 208-210°C.

La 7-(2-cloroetoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxiquinazolina usada como material de partida se obtuvo como sigue:-

Hexametildisilazano de sodio (solución 1M en THF, 164 ml) se agregó gota a gota durante una hora a una mezcla helada de 4-cloro-7-(2,4-dimetoxibenciloxi)-5-isopropoxiquinazolina (32 g), 4-amino-5-cloro-2,3-metilendioxipiridina (15.6 g) y THF (430 ml) manteniendo simultáneamente la temperatura de la mezcla de reacción a alrededor de 3°C. Al final de la adición, la mezcla de reacción se dejó calentar a temperatura ambiente y se agitó durante 2.5 horas. La mezcla de reacción se enfrió a 0°C y se agregó una mezcla de ácido acético (9.4 ml) y agua (250 ml). La mezcla se evaporó y el residuo se dividió en porciones entre

cloruro de metileno y agua, habiéndose ajustado la alcalinidad de la fase acuosa a 7.5 por la adición de una solución 3N de ácido clorhídrico acuoso. La fase orgánica se separó y la fase acuosa se extrajo tres veces con cloruro de metileno. Se combinaron las capas orgánicas, se lavaron con salmuera, se secaron sobre sulfato de magnesio y se evaporaron. El sólido resultante se trituró bajo acetato de etilo. Se obtuvo así 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(2,4-dimetoxibenciloxi)-5-isopropoxiquinazolina como un sólido blanco (38 g); Espectro de Masa: $M+H^+$ 525 y 527.

Trietilsilano (70 ml) y ácido trifluoroacético (48 ml) se agregaron en alternativamente a una solución helada de 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(2,4-dimetoxibenciloxi)-5-isopropoxiquinazolina (37.7 g) en cloruro de metileno (560 ml) y la mezcla de reacción resultante se agitó a temperatura ambiente durante 1 hora. Los disolventes se evaporaron bajo alto vacío. El sólido resultante se trituró bajo acetato de etilo. El material así obtenido se aisló, se lavó con acetato de etilo y se secó bajo alto vacío. Se obtuvo así la sal de ácido di-trifluoroacético (37.4 g) de 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-hidroxi-5-isopropoxiquinazolina, la cual se usó sin más purificación.

Carbonato de potasio (34.6 g) se agregó a una mezcla de 4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-hidroxi-5-isopropoxiquinazolina, sal de ácido di-trifluoroacético (49 g), 1,2-dicloroetano (440 ml) y DMF (245 ml) y la mezcla se agitó y se calentó a 90°C durante 3.5 horas. Se agregó una porción adicional (7 g) de carbonato de potasio y la mezcla se agitó a 90°C durante una hora más. La mezcla de reacción se enfrió a temperatura ambiente y los sólidos se extrajeron por filtración y se lavaron con cloruro de metileno. El filtrado y los desechos de lavado ***("washings")*** se combinaron y se evaporaron. El residuo resultante se purificó por cromatografía de columna en sílice usando mezclas crecientemente polares de cloruro de metileno y metanol (de una mezcla 50:1 a una mezcla 20:1) como eluyente. Se obtuvo así 7-(2-cloroetoxi)-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxiquinazolina como un sólido

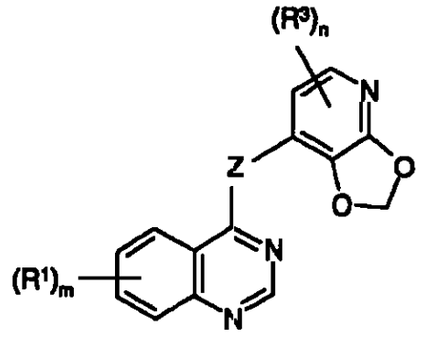
189

blanco (37.1 g); Espectro de Masa: $M+H^+$ 437 y 439.

190

REIVINDICACIONES

1. Un derivado de quinazolina de la Fórmula I



I

en donde **Z** es un grupo O, S, SO, SO_2, $N(R^2)$ ó $C(R^2)_2$ en donde cada grupo R^2, los cuales pueden ser los mismos o diferentes, es hidrógeno o (1-8C)alquilo;

m es 0, 1, 2 ó 3;

cada grupo R^1, los cuales pueden ser los mismos o diferentes, se selecciona de halógeno trifluorometilo, ciano, isociano, nitro, hidroxi, mercapto, amino, formilo, carboxi, carbamoilo, (1-8C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, (3-6C)alquenoilamino, N-(1-6C)alquil-(3-6C)alquenoilamino, (3-6C)alquinoilamino, N-(1-6C)alquil-(3-6C)alquinoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:

$$Q^1 - X^1 -$$

en donde X^1 es un enlace directo o se selecciona de O, S, SO, SO_2, $N(R^4)$, CO, $CH(OR^4)$, $CON(R^4)$, $N(R^4)CO$, $SO_2N(R^4)$, $N(R^4)SO_2$, $OC(R^4)_2$, $SC(R^4)_2$ y $N(R^4)C(R^4)_2$, en donde R^4 es hidrógeno o (1-8C)alquilo, y Q^1 es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo,

heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo, o $(R^1)_m$ es (1-3C)alquilenodioxi,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileno dentro de un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, S, SO, SO_2, $N(R^5)$, CO, $CH(OR^5)$, $CON(R^5)$, $N(R^5)CO$, $SO_2N(R^5)$, $N(R^5)SO_2$, CH=CH y C≡C en donde R^5 es hidrógeno o (1-8C)alquilo o, cuando el grupo insertado es $N(R^5)$, R^5 puede ser también (2-6C)alcanoilo,

y en donde cualquier grupo CH_2=CH- ó HC≡C- dentro de un sustituyente R^1 lleva opcionalmente en la posición terminal CH_2= o HC≡ un sustituyente seleccionado de halógeno carboxi, carbamoilo, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo y di-[(1-6C)alquil]amino-(1-6C)alquilo o de un grupo de la fórmula:

$$Q^2\text{-}X^2\text{-}$$

en donde X^2 es un enlace directo o se selecciona de CO y $N(R^6)CO$, en donde R^6 es hidrógeno o (1-8C)alquilo, y Q^2 es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde cualquier grupo CH_2 o CH_3 dentro de un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 o CH_3 uno o más sustituyente halógeno o (1-8C)alquilo o un sustituyente seleccionado de hidroxi, ciano, amino, carboxi, carbamoilo, oxo, tioxo, (1-6C)alcoxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:

$$-X^3\text{-}Q^3$$

en donde X^3 es un enlace directo o se selecciona de O, S, SO, SO_2, $N(R^7)$, CO, $CH(OR^7)$, $CON(R^7)$, $N(R^7)CO$, $SO_2N(R^7)$, $N(R^7)SO_2$, $C(R^7)_2O$, $C(R^7)_2S$ y $N(R^7)C(R^7)_2$, en donde R^7 es hidrógeno o (1-8C)alquilo, y Q^3 es arilo, aril-(1-6C)alquilo, (3-7C)cicloalquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo,

y en donde cualquier grupo arilo, heteroarilo o heterociclilo dentro de un sustituyente R^1 lleva opcionalmente 1, 2 ó 3 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de halógeno trifluorometilo, ciano, nitro, hidroxi, amino, carboxi, carbamoilo, (1-8C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino, N-(1-6C)alquil-(1-6C)alcanosulfonilamino y (1-3C)alquilenodioxi, o de un grupo de la fórmula:

$$-X^4-R^8$$

en donde X^4 es un enlace directo o se selecciona de O y $N(R^9)$, en donde R^9 es hidrógeno o (1-8C)alquilo, y R^8 es halógeno-(1-6C)alquilo, hidroxi-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo, di-[(1-6C)alquil]amino-(1-6C)alquilo, (2-6C)alcanoilamino-(1-6C)alquilo o (1-6C)alcoxicarbonilamino-(1-6C)alquilo, o de un grupo de la fórmula:

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

en donde X^5 es un enlace directo o se selecciona de O, $N(R^{10})$ y CO, en donde R^{10} es hidrógeno o (1-8C)alquilo, y Q^4 es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, los cuales pueden

ser los mismos o diferentes, seleccionados de halógeno (1-8C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo y (1-6C)alcoxi,

y en donde cualquier grupo heterociclilo dentro de un sustituyente R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo;

n es 0, 1, 2 ó 3; y

cada grupo R^3, los cuales pueden ser los mismos o diferentes, se selecciona de halógeno trifluorometilo, ciano, nitro, hidroxi, amino, carboxi, carbamoilo, (1-8C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo, (1-6C)alcoxi, (2-6C)alqueniloxi, (2-6C)alquiniloxi, (1-6C)alquiltio, (1-6C)alquilsulfinilo, (1-6C)alquilsulfonilo, (1-6C)alquilamino, di-[(1-6C)alquil]amino, (1-6C)alcoxicarbonilo, N-(1-6C)alquilcarbamoilo, N,N-di-[(1-6C)alquil]carbamoilo, (2-6C)alcanoilo, (2-6C)alcanoiloxi, (2-6C)alcanoilamino, N-(1-6C)alquil-(2-6C)alcanoilamino, (3-6C)alquenoilamino, N-(1-6C)alquil-(3-6C)alquenoilamino, (3-6C)alquinoilamino, N-(1-6C)alquil-(3-6C)alquinoilamino, N-(1-6C)alquilsulfamoilo, N,N-di-[(1-6C)alquil]sulfamoilo, (1-6C)alcanosulfonilamino y N-(1-6C)alquil-(1-6C)alcanosulfonilamino, o de un grupo de la fórmula:

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

en donde X^6 es un enlace directo o se selecciona de O y $N(R^{12})$, en donde R^{12} es hidrógeno o (1-8C)alquilo, y R^{11} es halógeno-(1-6C)alquilo, hidroxi-(1-6C)alquilo, (1-6C)alcoxi-(1-6C)alquilo, ciano-(1-6C)alquilo, amino-(1-6C)alquilo, (1-6C)alquilamino-(1-6C)alquilo o di-[(1-6C)alquil]amino-(1-6C)alquilo, o de un grupo de la fórmula:

$$-X^7 - Q^5$$

en donde X^7 es un enlace directo o se selecciona de O, S, SO, SO_2, $N(R^{13})$, CO, $CH(OR^{13})$, $CON(R^{13})$, $N(R^{13})CO$, $SO_2N(R^{13})$, $N(R^{13})SO_2$, $C(R^{13})_2O$, $C(R^{13})_2S$ y $N(R^{13})C(R^{13})_2$, en donde R^{13} es hidrógeno o (1-8C)alquilo, y Q^5 es arilo, aril-(1-6C)alquilo, heteroarilo, heteroaril-(1-6C)alquilo, heterociclilo o heterociclil-(1-6C)alquilo que lleva opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de halógeno (1-8C)alquilo, (2-8C)alquenilo, (2-8C)alquinilo y (1-6C)alcoxi,

y cualquier grupo heterociclilo dentro de Q^5 lleva opcionalmente 1 ó 2 sustituyentes oxo o tioxo;
o su sal farmacéuticamente aceptable.

2. Un derivado de quinazolina de la Fórmula I, o su sal farmacéuticamente aceptable, de acuerdo con la reivindicación 1, en donde Z es NH.

3. Un derivado de quinazolina de la Fórmula I, o su sal farmacéuticamente aceptable, de acuerdo con la reivindicación 1, en donde m es 1 y el grupo R^1 se localiza en la posición 5, 6 ó 7 ó m es 2 y los grupos R^1, los cuales pueden ser los mismos o diferentes, se localizan en las posiciones 5 y 7 ó en las posiciones 6 y 7 y cada R^1 se selecciona de hidroxi, amino, metilo, etilo, propilo, butilo, vinilo, etinilo, metoxi, etoxi, propoxi, isopropoxi, butoxi, pentiloxi, but-3-eniloxi, pent-4-eniloxi, hex-5-eniloxi, but-3-iniloxi, pent-4-iniloxi, hex-5-iniloxi, metilamino, etilamino, dimetilamino, dietilamino, acetamido, propionamido, ciclopentiloxi, ciclohexiloxi, fenoxi, benciloxi, tetrahidrofuran-3-iloxi, tetrahidropiran-3-iloxi, tetrahidropiran-4-iloxi, ciclopropilmetoxi, 2-imidazol-1-iletoxi, 3-imidazol-1-ilpropoxi, 2-(1,2,3-triazol-1-il)etoxi, 3-(1,2,3-triazol-1-il)propoxi, 2-(1,2,4-triazol-1-il)etoxi, 3-(1,2,4-triazol-1-il)propoxi, pirid-2-ilmetoxi, pirid-3-ilmetoxi, pirid-4-ilmetoxi, 2-pirid-2-iletoxi, 2-pirid-3-iletoxi, 2-pirid-4-iletoxi, 3-pirid-2-ilpropoxi, 3-pirid-3-ilpropoxi, 3-pirid-4-ilpropoxi, pirrolidin-1-ilo, morfolino, piperidino, piperazin-1-ilo, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 4-pirrolidin-1-ilbutoxi, pirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 2-pirrolidin-2-iletoxi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 4-morfolinobutoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 4-piperidinobutoxi, piperidin-3-iloxi, piperidin-4-iloxi, piperidin-3-ilmetoxi, piperidin-4-ilmetoxi, 2-piperidin-3-iletoxi, 3-piperidin-3-ilpropoxi, 2-piperidin-4-iletoxi, 3-piperidin-4-ilpropoxi, 2-homopiperidin-1-iletoxi, 3-

homopiperidin-1-ilpropoxi, 2-(1,2,3,6-tetrahidropiridin-1-il)etoxi 3-(1,2,3,6-tetrahidropiridin-1-il)propoxi, 4-(1,2,3,6-tetrahidropiridin-1-il)butoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 4-piperazin-1-ilbutoxi, 2-homopiperazin-1-iletoxi, 3-homopiperazin-1-ilpropoxi, 2-pirrolidin-1-iletilamino, 3-pirrolidin-1-ilpropilamino, 4-pirrolidin-1-ilbutilamino, pirrolidin-3-ilamino, pirrolidin-2-ilmetilamino, 2-pirrolidin-2-iletilamino, 3-pirrolidin-2-ilpropilamino, 2-morfolinoetilamino, 3-morfolinopropilamino, 4-morfolinobutilamino, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etilamino, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propilamino, 2-piperidinoetilamino, 3-piperidinopropilamino, 4-piperidinobutilamino, piperidin-3-ilamino, piperidin-4-ilamino, piperidin-3-ilmetilamino, 2-piperidin-3-iletilamino, piperidin-4-ilmetilamino, 2-piperidin-4-iletilamino, 2-homopiperidin-1-iletilamino, 3-homopiperidin-1-ilpropilamino, 2-piperazin-1-iletilamino, 3-piperazin-1-ilpropilamino, 4-piperazin-1-ilbutilamino, 2-homopiperazin-1-iletilamino ó 3-homopiperazin-1-ilpropilamino,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileno dentro de un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH, N(Me), CH=CH y C≡C,

y cuando R^1 es un grupo vinilo etinilo, el sustituyente R^1 lleva opcionalmente en la posición terminal CH_2= ó HC≡ un sustituyente seleccionado de N-(2-dimetilaminoetil)carbamoilo, N-(3-dimetilaminopropil)carbamoilo, metilaminometilo, 2-metilaminoetilo, 3-metilaminopropilo, 4-metilaminobutilo, dimetilaminometilo, 2-dimetilaminoetilo, 3-dimetilaminopropilo y 4-dimetilaminobutilo, o de un grupo de la fórmula:

$$Q^2\text{-}X^2\text{-}$$

en donde X^2 es un enlace directo o es NHCO o N(Me)CO y Q^2 es imidazolilmetilo, 2-imidazoliletilo, 3-imidazolilpropilo, piridilmetilo, 2-piridiletilo, 3-piridilpropilo, pirrolidin-1-ilmetilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, 4-pirrolidin-1-ilbutilo, pirrolidin-2-ilmetilo, 2-

pirrolidin-2-iletilo, 3-pirrolidin-2-ilpropilo, morfolinometilo, 2-morfolinoetilo, 3-morfolinopropilo, 4-morfolinobutilo, piperidinometilo, 2-piperidinoetilo, 3-piperidinopropilo, 4-piperidinobutilo, piperidin-3-ilmetilo, 2-piperidin-3-iletilo, piperidin-4-ilmetilo, 2-piperidin-4-iletilo, piperazin-1-ilmetilo, 2-piperazin-1-iletilo, 3-piperazin-1-ilpropilo ó 4-piperazin-1-ilbutilo,

y en donde cualquier grupo CH_2 ó CH_3 dentro de un sustituyente R^1 lleva opcionalmente en cada dicho en cada dicho grupo CH_2 o CH_3 uno o más grupos fluoro o cloro o un sustituyente seleccionado de hidroxi, oxo, amino, metoxi, metilsulfonilo, metilamino, dimetilamino, diisopropilamino, N-etil-N-metilamino, N-isopropil-N-metilamino, N-metil-N-propilamino, acetoxi, acetamido y N-metilacetamido,

y en donde cualquier grupo fenilo, imidazolilo, triazolilo, piridilo o heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxi, amino, carbamoilo, metilo, etilo, metoxi, etoxi, N-metilcarbamoilo, N,N-dimetilcarbamoilo, metilendioxi, etilidendioxi y isopropilidendioxi, y un grupo pirrolidin-2-ilo, piperidin-3-ilo, piperidin-4-ilo, piperazin-1-ilo u homopiperazin-1-ilo dentro de un sustituyente R^1 se N-sustituye opcionalmente con alilo, 2-propinilo, metilsulfonilo, etilsulfonilo, acetilo, propionilo, isobutirilo, 2-fluoroetilo, 2,2-difluoroetilo, 2,2,2-trifluoroetilo, 3-fluoropropilo, 3,3-difluoropropilo, 3,3,3-trifluoropropilo, 2-metoxietilo, 3-metoxipropilo, cianometilo, 2-aminoetilo, 3-aminopropilo, 2-metilaminoetilo, 3-metilaminopropilo, 2-dimetilaminoetilo, 3-dimetilaminopropilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, 2-morfolinoetilo, 3-morfolinopropilo, 2-piperidinoetilo, 3-piperidinopropilo, 2-piperazin-1-iletilo ó 3-piperazin-1-ilpropilo, cuyos últimos 8 sustituyentes lleva cada uno opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, metilo y metoxi,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo.

4. Un derivado de quinazolina de la Fórmula I, o su sal farmacéuticamente aceptable, de acuerdo con la reivindicación 1, en donde m es 1 y el grupo R^1 se localiza en la posición 5 ó m es 2 y los grupos R^1, los cuales pueden ser los mismos o diferentes, se localizan en las posiciones 5 y 7 y cada R^1 se seleccionan de hidroxi, amino, metilo, etilo, metoxi, etoxi, propoxi, isopropoxi, butoxi, metilamino, etilamino, dimetilamino, dietilamino, acetamido, tetrahidrofuran-3-iloxi, tetrahidropiran-4-iloxi, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 4-pirrolidin-1-ilbutoxi, pirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 2-pirrolidin-2-iletoxi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 4-morfolinobutoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 4-piperidinobutoxi, 3-piperidiniloxi, 4-piperidiniloxi, piperidin-3-ilmetoxi, piperidin-4-ilmetoxi, 2-piperidin-3-iletoxi, 2-piperidin-4-iletoxi, 2-homopiperidin-1-iletoxi, 3-homopiperidin-1-ilpropoxi, 3-(1,2,3,6-tetrahidropiridin-1-il)propoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-homopiperazin-1-iletoxi, 3-homopiperazin-1-ilpropoxi, ciclobutiloxi, ciclopentiloxi y ciclohexiloxi,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileno dentro de un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH, CH=CH y C≡C,

y en donde cualquier grupo CH_2 ó CH_3 dentro de un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 uno o más grupos cloro o un sustituyente seleccionado de hidroxi, oxo, amino, metoxi, metilsulfonilo, metilamino, dimetilamino, diisopropilamino, N-etil-N-metilamino, N-isopropil-N-metilamino y acetoxi,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxi, amino, metilo, etilo, metoxi, metilendioxi, etilidendioxi y isopropilidendioxi, y un grupo pirrolidin-2-ilo, pirrolidin-3-ilo, piperidin-3-

198

ilo, piperidin-4-ilo, piperazin-1-ilo u homopiperazin-1-ilo dentro de un sustituyente R^1 se N-sustituye opcionalmente con metilo, etilo, propilo, alilo, 2-propinilo, metilsulfonilo, acetilo, propionilo, isobutirilo, 2-fluoroetilo, 2,2-difluoroetilo, 2,2,2-trifluoroetilo o cianometilo,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo.

5. Un derivado de quinazolina de la Fórmula I, o su sal farmacéuticamente aceptable, de acuerdo con la reivindicación 1, en donde m es 2 y los grupos R^1, los cuales pueden ser los mismos o diferentes, se localizan en las posiciones 5 y 7 y el grupo R^1 en la posición 5 se selecciona de metoxi, etoxi, propoxi, isopropoxi, butoxi, tetrahidrofuran-3-iloxi, tetrahidropiran-4-iloxi, pirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 3-piperidiniloxi, 4-piperidiniloxi, piperidin-3-ilmetoxi, piperidin-4-ilmetoxi, ciclobutiloxi, ciclopentiloxi y ciclohexiloxi, y el grupo R^1 en la posición 7 se selecciona de hidroxi, metoxi, etoxi, propoxi, isopropoxi, butoxi, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 4-pirrolidin-1-ilbutoxi, 2-pirrolidin-2-iletoxi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 4-morfolinobutoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 4-piperidinobutoxi, 2-piperidin-3-iletoxi, 2-piperidin-4-iletoxi, 2-homopiperidin-1-iletoxi, 3-homopiperidin-1-ilpropoxi, 3-(1,2,3,6-tetrahidropiridin-1-il)propoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-homopiperazin-1-iletoxi y 3-homopiperazin-1-ilpropoxi,

y en donde cualquier grupo CH_2 ó CH_3 dentro de un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 uno o más grupos cloro o un sustituyente seleccionado de hidroxi, oxo, amino, metoxi, metilsulfonilo, metilamino, dimetilamino, diisopropilamino, N-etil-N-metilamino, N-isopropil-N-metilamino y acetoxi,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los

mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxi, amino, metilo, etilo, metoxi, metilendioxi, etilidendioxi e isopropilidendioxi, y un grupo pirrolidin-2-ilo, pirrolidin-3-ilo, piperidin-3-ilo, piperidin-4-ilo, piperazin-1-ilo u homopiperazin-1-ilo dentro de un sustituyente R^1 se N-sustituye opcionalmente con metilo, etilo, propilo, alilo, 2-propinilo, metilsulfonilo, acetilo, propionilo, isobutirilo, 2-fluoroetilo, 2,2-difluoroetilo, 2,2,2-trifluoroetilo o cianometilo,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo.

6. Un derivado de quinazolina de la Fórmula I, o su sal farmacéuticamente aceptable, de acuerdo con la reivindicación 1, en donde n es 1 y el grupo R^3 se localiza en la posición 5 del grupo 2,3-metilendioxipiridin-4-ilo y se selecciona de fluoro, cloro, bromo, trifluorometilo, ciano, hidroxi, metilo, etilo, metoxi y etoxi.

7. Un derivado de quinazolina de la Fórmula I de acuerdo con la reivindicación 1 en donde:-

Z es O ó NH;

m es 1 y el grupo R^1 se localiza en la posición 5, 6 ó 7 o m es 2 y los grupos R^1, los cuales pueden ser los mismos o diferentes, se localizan en las posiciones 5 y 7 o en las posiciones 6 y 7 y cada R^1 se selecciona de hidroxi, amino, metilo, etilo, propilo, butilo, vinilo, etinilo, metoxi, etoxi, propoxi, isopropoxi, butoxi, pentiloxi, but-3-eniloxi, pent-4-eniloxi, hex-5-eniloxi, but-3-iniloxi, pent-4-iniloxi, hex-5-iniloxi, metilamino, etilamino, dimetilamino, dietilamino, acetamido, propionamido, ciclopentiloxi, ciclohexiloxi, fenoxi, benciloxi, tetrahidrofuran-3-iloxi, tetrahidropiran-3-iloxi, tetrahidropiran-4-iloxi, ciclopropilmetoxi, 2-imidazol-1-iletoxi, 3-imidazol-1-ilpropoxi, 2-(1,2,3-triazol-1-il)etoxi, 3-(1,2,3-triazol-1-il)propoxi, 2-(1,2,4-triazol-1-il)etoxi, 3(1,2,4-triazol-1-il)propoxi, pirid-2-ilmetoxi, pirid-3-ilmetoxi, pirid-4-ilmetoxi, 2-pirid-2-iletoxi, 2-pirid-3-iletoxi, 2-pirid-4-iletoxi, 3-pirid-2-ilpropoxi, 3-pirid-3-ilpropoxi, 3-pirid-4-

ilpropoxi, pirrolidin-1-ilo, morfolino, piperidino, piperazin-1-ilo, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 4-pirrolidin-1-ilbutoxi, pirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 2-pirrolidin-2-iletoxi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 4-morfolinbutoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 4-piperidinobutoxi, piperidin-3-iloxi, piperidin-4-iloxi, piperidin-3-ilmetoxi, piperidin-4-ilmetoxi, 2-piperidin-3-iletoxi, 3-piperidin-3-ilpropoxi, 2-piperidin-4-iletoxi,3-piperidin-4-ilpropoxi, 2-homopiperidin-1-iletoxi, 3-homopiperidin-1-ilpropoxi, 2-(1,2,3,6-tetrahidropiridin-1-il)etoxi 3-(1,2,3,6-tetrahidropiridin-1-il)propoxi, 4-(1,2,3,6-tetrahidropiridin-1-il)butoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 4-piperazin-1-ilbutoxi, 2-homopiperazin-1-iletoxi, 3-homopiperazin-1-ilpropoxi, 2-pirrolidin-1-iletilamino, 3-pirrolidin-1-ilpropilamino, 4-pirrolidin-1-ilbutilamino, pirrolidin-3-ilamino, pirrolidin-2-ilmetilamino, 2-pirrolidin-2-iletilamino, 3-pirrolidin-2-ilpropilamino, 2-morfolinoetilamino, 3-morfolinopropilamino, 4-morfolinobutilamino, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etilamino, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propilamino, 2-piperidinoetilamino, 3-piperidinopropilamino, 4-piperidinobutilamino, piperidin-3-ilamino, piperidin-4-ilamino, piperidin-3-ilmetilamino, 2-piperidin-3-iletilamino, piperidin-4-ilmetilamino, 2-piperidin-4-iletilamino, 2-homopiperidin-1-iletilamino, 3-homopiperidin-1-ilpropilamino, 2-piperazin-1-iletilamino, 3-piperazin-1-ilpropilamino, 4-piperazin-1-ilbutilamino, 2-homopiperazin-1-iletilamino o 3-homopiperazin-1-ilpropilamino,

y en donde átomos de carbono adyacentes en cualquier cadena (2-6C)alquileno dentro de un sustituyente R^1 se separan opcionalmente por la inserción en la cadena de un grupo seleccionado de O, NH, N(Me), CH=CH y C≡C,

y cuando R^1 es un grupo vinilo o etinilo, el sustituyente R^1 lleva opcionalmente en la posición terminal CH_2= o HC≡ un substituyente seleccionado de N-(2-dimetilaminoetil)carbamoilo, N-(3-

dimetilaminopropil)carbamoilo, metilaminometilo, 2-metilaminoetilo, 3-metilaminopropilo, 4-metilaminobutilo, dimetilaminometilo, 2-dimetilaminoetilo, 3-dimetilaminopropilo y 4-dimetilaminobutilo, o de un grupo de la fórmula

$$Q^2\text{-}X^2\text{-}$$

en donde X^2 es un enlace directo o es NHCO o N(Me)CO y Q^2 es imidazolilmetilo, 2-imidazoliletilo, 3-imidazolilpropilo, piridilmetilo, 2-piridiletilo, 3-piridilpropilo, pirrolidin-1-ilmetilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, 4-pirrolidin-1-ilbutilo, pirrolidin-2-ilmetilo, 2-pirrolidin-2-iletilo, 3-pirrolidin-2-ilpropilo, morfolinometilo, 2-morfolinoetilo, 3-morfolinopropilo, 4-morfolinobutilo, piperidinometilo, 2-piperidinoetilo, 3-piperidinopropilo, 4-piperidinobutilo, piperidin-3-ilmetilo, 2-piperidin-3-iletilo, piperidin-4-ilmetilo, 2-piperidin-4-iletilo, piperazin-1-ilmetilo, 2-piperazin-1-iletilo, 3-piperazin-1-ilpropilo o 4-piperazin-1-ilbutilo,

y en donde cualquier grupo CH_2 ó CH_3 dentro de un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 uno o más grupos fluoro o cloro o un sustituyente seleccionado de hidroxi, oxo, amino, metoxi, metilsulfonilo, metilamino, dimetilamino, diisopropilamino, N-etil-N-metilamino, N-isopropil-H-metilamino, N-metil-N-propilamino, acetoxi, acetamido y N-metilacetamido,

y en donde cualquier grupo fenilo, imidazolilo, triazolilo, piridilo o heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxi, amino, carbamoilo, metilo, etilo, metoxi, etoxi, N-metilcarbamoilo, N,N-dimetilcarbamoilo, metilendioxi, etilidendioxi e isopropilidendioxi, y un grupo pirrolidin-2-ilo, piperidin-3-ilo, piperidin-4-ilo, piperazin-1-ilo u homopiperazin-1-ilo dentro de un sustituyente R^1 se N-sustituye opcionalmente con alilo, 2-propinilo, metilsulfonilo, etilsulfonilo, acetilo, propionilo, isobutirilo, 2-fluoroetilo, 2,2-difluoroetilo, 2,2,2-trifluoroetilo, 3-fluoropropilo, 3,3-difluoropropilo, 3,3,3-trifluoropropilo, 2-metoxietilo, 3-metoxipropilo, cianometilo, 2-

aminoetilo, 3-aminopropilo, 2-metilaminoetilo, 3-metilaminopropilo, 2-dimetilaminoetilo, 3-dimetilaminopropilo, 2-pirrolidin-1-iletilo, 3-pirrolidin-1-ilpropilo, 2-morfolinoetilo, 3-morfolinopropilo, 2-piperidinoetilo, 3-piperidinopropilo, 2-piperazin-1-iletilo ó 3-piperazin-1-ilpropilo, cuyos últimos 8 sustituyentes lleva cada uno opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, metilo y metoxi,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo;

n es 0 ó n es 1 y el grupo R^3 se localiza en la posición 5 ó 6 del grupo 2,3-metilendioxipiridin-4-ilo y se selecciona de fluoro, cloro, bromo, trifluorometilo, ciano, hidroxi, metilo, etilo, metoxi y etoxi;

o su sal de adición de ácido farmacéuticamente aceptable.

8. Un derivado de quinazolina de la Fórmula I de acuerdo con la reivindicación 1en donde:-

Z es NH;

m es 2 y el primer grupo R^1 es un grupo 6-metoxi y el segundo grupo R^1 se localiza en la posición 7 y se selecciona de 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]etoxi, 3-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]propoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-piperidin-3-iletoxi, 2-(N-metilpiperidin-3-il)etoxi, 3-piperidin-3-ilpropoxi, 3-(N-metilpiperidin-3-il)propoxi, 2-piperidin-4-iletoxi, 2-(N-metilpiperidin-4-il)etoxi, 3-piperidin-4-ilpropoxi, 3-(N-metilpiperidin-4-il)propoxi, 2-(1,2,3,6-tetrahidropiridin-1-il)etoxi, 3-(1,2,3,6-tetrahidropiridin-1-il)propoxi, 2-(4-hidroxipiperidin-1-il)etoxi, 3-(4-hidroxipiperidin-1-il)propoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 4-piperazin-1-ilbutoxi, 2-(4-metilpiperazin-1-il)etoxi, 3-(4-metilpiperazin-1-il)propoxi, 4-(4-metilpiperazin-1-il)butoxi, 2-(4-alilpiperazin-1-il)etoxi, 3-(4-alilpiperazin-1-il)propoxi, 2-(4-prop-2-

inilpiperazin-1-il)etoxi, 3-(4-prop-2-inilpiperazin-1-il)propoxi, 2-(4-metilsulfonilpiperazin-1-il)etoxi, 3-(4-metilsulfonilpiperazin-1-il)propoxi, 2-(4-acetilpiperazin-1-il)etoxi, 3-(4-acetilpiperazin-1-il)propoxi, 4-(4-acetilpiperazin-1-il)butoxi, 2-(4-isobutirilpiperazin-1-il)etoxi, 3-(4-isobutirilpiperazin-1-il)propoxi, 4-(4-isobutirilpiperazin-1-il)butoxi, 2-[4-(2-fluoroetil)piperazin-1-il]etoxi, 3-[4-(2-fluoroetil)piperazin-1-il]propoxi, 2-[4-(2,2,2-trifluoroetil)piperazin-1-il]etoxi, 3-[4-(2,2,2-trifluoroetil)piperazin-1-il]propoxi, 2-(4-cianometilpiperazin-1-il)etoxi, 3-(4-cianometilpiperazin-1-il)propoxi, 2-[2-(4-metilpiperazin-1-il)etoxi]etoxi, 2-cloroetoxi, 3-cloropropoxi, 4-clorobutoxi, 2-metilsulfoniletoxi, 3-metilsulfonilpropoxi, 2-(2-metoxietoxi)etoxi, 2-(4-piridiloxi)etoxi, 3-piridilmetoxi y 2-cianopirid-4-ilmetoxi; y

n es 0 ó n es 1 y el grupo R3 se localiza en la posición 5 ó 6 del grupo 2,3-metilendioxipiridin-4-ilo y se selecciona de fluoro, cloro, bromo, trifluorometilo y ciano;

o su sal de adición de ácido farmacéuticamente aceptable.

9. Un derivado de quinazolina de la Fórmula I de acuerdo con la reivindicación 1 en donde:-

Z es NH;

m es 2 y los grupos R^1, los cuales pueden ser los mismos o diferentes, se localizan en las posiciones 5 y 7 y el grupo R^1 en la posición 5 se selecciona de metoxi, etoxi, propoxi, isopropoxi, butoxi, tetrahidrofuran-3-iloxi, tetrahidropiran-4-iloxi, pirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 3-piperidiniloxi, 4-piperidiniloxi, piperidin-3-ilmetoxi, piperidin-4-ilmetoxi, ciclobutiloxi, ciclopentiloxi y ciclohexiloxi, y el grupo R^1 en la posición 7 se selecciona de hidroxi, metoxi, etoxi, propoxi, isopropoxi, butoxi, 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 4-pirrolidin-1-ilbutoxi, 2-pirrolidin-2-iletoxi, 3-pirrolidin-2-ilpropoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 4-morfolinobutoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 4-piperidinobutoxi, 2-piperidin-3-

iletoxi, 2-piperidin-4-iletoxi, 2-homopiperidin-1-iletoxi, 3-homopiperidin-1-ilpropoxi, 3-(1,2,3,6-tetrahidropiridin-1-il)propoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-homopiperazin-1-iletoxi y 3-homopiperazin-1-ilpropoxi,

y en donde cualquier grupo CH_2 ó CH_3 dentro de un sustituyente R^1 lleva opcionalmente en cada dicho grupo CH_2 ó CH_3 uno o más grupos cloro o un sustituyente seleccionado de hidroxi, oxo, amino, metoxi, metilsulfonilo, metilamino, dimetilamino, diisopropilamino, N-etil-N-metilamino, N-isopropil-N-metilamino y acetoxi,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de fluoro, cloro, trifluorometilo, hidroxi, amino, metilo, etilo, metoxi, metilendioxi, etilidendioxi e isopropilidendioxi, y un grupo pirrolidin-2-ilo, pirrolidin-3-ilo, piperidin-3-ilo, piperidin-4-ilo, piperazin-1-ilo o homopiperazin-1-ilo dentro de un sustituyente R^1 se N-sustituye opcionalmente con metilo, etilo, propilo, alilo, 2-propinilo, metilsulfonilo, acetilo, propionilo, isobutirilo, 2-fluoroetilo, 2,2-difluoroetilo, 2,2,2-trifluoroetiloo cianometilo,

y en donde cualquier grupo heterociclilo dentro de un sustituyente en R^1 lleva opcionalmente 1 ó 2 sustituyentes oxo;

n es 0 ó n es 1 y el grupo R^3 se localiza en la posición 5 ó 6 del grupo 2,3-metilendioxipiridin-4-ilo y se selecciona de fluoro, cloro, bromo, trifluorometilo, ciano, hidroxi, metilo, etilo, metoxi y etoxi;
o su sal de adición de ácido farmacéuticamente aceptable.

10. Un derivado de quinazolina de la Fórmula I de acuerdo con la reivindicación 1 en donde:-

Z es NH;

m es 1 y el grupo R^1 se localiza en la posición 5 y se selecciona de propoxi, isopropoxi, tetrahidrofuran-3-iloxi, tetrahidropiran-4-iloxi, pirrolidin-3-iloxi, N-metilpirrolidin-3-iloxi, pirrolidin-2-ilmetoxi, 3-piperidiniloxi, N-metilpiperidin-3-iloxi, 4-piperidiniloxi, N-metilpiperidin-

4-iloxi, N-alilpiperidin-4-iloxi, N-prop-2-inilpiperidin-4-iloxi, N-acetilpiperidin-4-iloxi, N-metilsulfonilpiperidin-4-iloxi, piperidin-3-ilmetoxi, N-metilpiperidin-3-ilmetoxi, piperidin-4-ilmetoxi, N-metilpiperidin-4-ilmetoxi, ciclobutiloxi, ciclopentiloxi y ciclohexiloxi,

ó m es 2 y el primer grupo R^1 se localiza en la posición 5 y se selecciona del grupo de sustituyentes listado inmediatamente arriba y el segundo grupo R^1 se localiza en la posición 7 y se selecciona de 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]etoxi, 3-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]propoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)etoxi, 3-(1,1-dioxotetrahidro-4H-1,4-tiazin-4-il)propoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-piperidin-3-iletoxi, 2-(N-metilpiperidin-3-il)etoxi, 3-piperidin-3-ilpropoxi, 3-(N-metilpiperidin-3-il)propoxi, 2-piperidin-4-iletoxi, 2-(N-metilpiperidin-4-il)etoxi, 3-piperidin-4-ilpropoxi, 3-(N-metilpiperidin-4-il)propoxi, 2-(1,2,3,6-tetrahidropiridin-1-il)etoxi, 3-(1,2,3,6-tetrahidropiridin-1-il)propoxi, 2-(4-hidroxipiperidin-1-il)etoxi, 3-(4-hidroxipiperidin-1-il)propoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 4-piperazin-1-ilbutoxi, 2-(4-metilpiperazin-1-il)etoxi, 3-(4-metilpiperazin-1-il)propoxi, 4-(4-metilpiperazin-1-il)butoxi, 2-(4-alilpiperazin-1-il)etoxi, 3-(4-alilpiperazin-1-il)propoxi, 2-(4-prop-2-inilpiperazin-1-il)etoxi, 3-(4-prop-2-inilpiperazin-1-il)propoxi, 2-(4-metilsulfonilpiperazin-1-il)etoxi, 3-(4-metilsulfonilpiperazin-1-il)propoxi, 2-(4-acetilpiperazin-1-il)etoxi, 3-(4-acetilpiperazin-1-il)propoxi, 4-(4-acetilpiperazin-1-il)butoxi, 2-(4-isobutirilpiperazin-1-il)etoxi, 3-(4-isobutirilpiperazin-1-il)propoxi, 4-(4-isobutirilpiperazin-1-il)butoxi, 2-[4-(2-fluoroetil)piperazin-1-il]etoxi, 3-[4-(2-fluoroetil)piperazin-1-il]propoxi, 2-[4-(2,2,2-trifluoroetil)piperazin-1-il]etoxi, 3-[4-(2,2,2-trifluoroetil)piperazin-1-il]propoxi, 2-(4-cianometilpiperazin-1-il)etoxi, 3-(4-cianometilpiperazin-1-il)propoxi, 2-[2-(4-metilpiperazin-1-il)etoxi]etoxi, 2-cloroetoxi, 3-cloropropoxi, 4-clorobutoxi, 2-metilsulfoniletoxi, 3-metilsulfonilpropoxi, 2-(2-metoxietoxi)etoxi, 2-(4-piridiloxi)etoxi, 3-piridilmetoxi y 2-cianopirid-4-ilmetoxi;

n es 0 ó n es 1 y el grupo R^3 se localiza en la posición 5 ó 6 del grupo 2,3-metilendioxipiridin-4-ilo y se selecciona de cloro, bromo, trifluorometilo, ciano, hidroxi, metilo, etilo, metoxi y etoxi; o su sal de adición de ácido farmacéuticamente aceptable.

11. Un derivado de quinazolina de la Fórmula I de acuerdo con la reivindicación 1 en donde:-

Z es NH;

m es 2 y el primer grupo R1 se localiza en la posición 5 y se selecciona de isopropoxi y tetrahidropiran-4-iloxi, y el segundo grupo R1 se localiza en la posición 7 y se selecciona de 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]etoxi, 3-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]propoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-piperazin-1-iletoxi, 3-piperazin-1-ilpropoxi, 2-(4-metilpiperazin-1-il)etoxi, 3-(4-metilpiperazin-1-il)propoxi, 2-(4-alilpiperazin-1-il)etoxi, 3-(4-alilpiperazin-1-il)propoxi, 2-(4-prop-2-inilpiperazin-1-il)etoxi, 3-(4-prop-2-inilpiperazin-1-il)propoxi, 2-(4-acetilpiperazin-1-il)etoxi, 3-(4-acetilpiperazin-1-il)propoxi, 2-(4-isobutirilpiperazin-1-il)etoxi, 3-(4-isobutirilpiperazin-1-il)propoxi, 2-[4-(2-hidroxietil)piperazin-1-il]etoxi, 3-[4-(2-hidroxietil)piperazin-1-il]propoxi, 2-[4-(2,2,2-trifluoroetil)piperazin-1-il]etoxi, 3-[4-(2,2,2-trifluoroetil)piperazin-1-il]propoxi, 2-[4-(2-dimetilaminoacetil)piperazin-1-il]etoxi y 3-[4-(2-dimetilaminoacetil)piperazin-1-il]propoxi; y

n es 1 y el grupo R^3 se localiza en la posición 5 del grupo 2,3-metilendioxipiridin-4-ilo y se selecciona de cloro y bromo;
o su sal de adición de ácido farmacéuticamente aceptable.

12. Un derivado de quinazolina de la Fórmula I de acuerdo con la reivindicación 1 en donde:-

Z es NH;

m es 2 y el primer grupo R^1 se localiza en la posición 5 y se

selecciona de isopropoxi y tetrahidropiran-4-iloxi, y el segundo grupo R^1 se localiza en la posición 7 y se selecciona de 2-pirrolidin-1-iletoxi, 3-pirrolidin-1-ilpropoxi, 2-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]etoxi, 3-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]propoxi,2-morfolinoetoxi, 3-morfolinopropoxi, 2-piperidinoetoxi, 3-piperidinopropoxi, 2-(4-metilpiperazin-1-il)etoxi, 3-(4-metilpiperazin-1-il)propoxi, 2-(4-alilpiperazin-1-il)etoxi, 3-(4-alilpiperazin-1-il)propoxi, 2-(4-prop-2-inilpiperazin-1-il)etoxi, 3-(4-prop-2-inilpiperazin-1-il)propoxi, 2-(4-acetilpiperazin-1-il)etoxi, 3-(4-acetilpiperazin-1-il)propoxi, 2-(4-isobutirilpiperazin-1-il)etoxi, 3-(4-isobutirilpiperazin-1-il)propoxi, 2-[4-(2,2,2-trifluoroetil)piperazin-1-il]etoxi y 3-[4-(2,2,2-trifluoroetil)piperazin-1-il]propoxi; y

n es 1 y el grupo R^3 se localiza en la posición 5 del grupo 2,3-metilendioxipiridin-4-ilo y se selecciona de cloro y bromo;
o su sal de adición de ácido farmacéuticamente aceptable.

13. Un derivado de quinazolina de la Fórmula I de acuerdo con la reivindicación 1 en donde:-

Z es NH;

m es 2 y el primer grupo R^1 se localiza en la posición 5 y se selecciona de isopropoxi y tetrahidropiran-4-iloxi, y el segundo grupo R^1 se localiza en la posición 7 y se selecciona de 2-pirrolidin-1-iletoxi, 2-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]etoxi, 2-morfolinoetoxi, 3-morfolinopropoxi, 2-piperidinoetoxi, 2-piperazin-1-iletoxi, 2-(4-metilpiperazin-1-il)etoxi, 2-(4-prop-2-inilpiperazin-1-il)etoxi, 3-(4-prop-2-inilpiperazin-1-il)propoxi, 2-(4-acetilpiperazin-1-il)etoxi, 2-[4-(2-hidroxietil)piperazin-1-il]etoxi y 2-[4-(2-dimetilaminoacetil)piperazin-1-il]etoxi; y

n es 1 y el grupo R^3 se localiza en la posición 5 del grupo 2,3-metilendioxipiridin-4-ilo y es un grupo cloro;
o su sal de adición de ácido farmacéuticamente aceptable.

14. Un derivado de quinazolina de la Fórmula I de acuerdo con la reivindicación 1 en donde:-

Z es NH;

m es 2 y el primer grupo R1 es un grupo 5-isopropoxi y el segundo grupo R^1 se localiza en la posición 7 y se selecciona de 2-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]etoxi, 2-piperazin-1-iletoxi, 2-(4-metilpiperazin-1-il)etoxi, 2-(4-acetilpiperazin-1-il)etoxi y 2-[4-(2-hidroxietil)piperazin-1-il]etoxi; y

n es 1 y el grupo R^3 se localiza en la posición 5 del grupo 2,3-metilendioxipiridin-4-ilo y es un grupo cloro;
o su sal de adición de ácido farmacéuticamente aceptable.

15. Un derivado de quinazolina de la Fórmula I de acuerdo con la reivindicación 1 seleccionado de:-
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-metoxi-7-[3-(4-prop-2-inilpiperazin-1-il)propoxi]quinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-[3-(4-isobutirilpiperazin-1-il)propoxi]-6-metoxiquinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-metoxi-7-{3-[4-(2,2,2-trifluoroetil)piperazin-1-il]propoxi}quinazolina y
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-6-metoxi-7-[2-(4-prop-2-inilpiperazin-1-il)etoxi]quinazolina;
o su sal de adición de ácido farmacéuticamente aceptable.

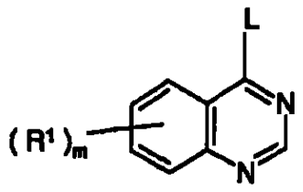
16. Un derivado de quinazolina de la Fórmula I de acuerdo con la reivindicación 1, seleccionado de:-
7-[2-(4-acetilpiperazin-1-il)etoxi]-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-tetrahidropiran-4-iloxiquinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-{2-[(3RS,4SR)-3,4-metilendioxipirrolidin-1-il]etoxi}-5-tetrahidropiran-4-iloxiquinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-[2-(4-prop-2-inilpiperazin-1-il)etoxi]-5-tetrahidropiran-4-iloxiquinazolina,

4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-[3-(4-prop-2-inilpiperazin-1-il)propoxi]-5-tetrahidropiran-4-iloxiquinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(2-morfolinoetoxi)-5-tetrahidropiran-4-iloxiquinazolina y
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-(3-morfolinopropoxi)-5-tetrahidropiran-4-iloxiquinazolina;
o su sal de adición de ácido farmacéuticamente aceptable.

17. Un derivado de quinazolina de la Fórmula I de acuerdo con la reivindicación 1, seleccionado de:-
7-[2-(4-acetilpiperazin-1-il)etoxi]-4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxiquinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxi-7-(2-piperazin-1-iletoxi)quinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-{2-[4-(2-hidroxietil) piperazin-1-il]etoxi}-5-isopropoxiquinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxi-7-(2-pirrolidin-1-iletoxi)quinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxi-7-(2-piperidinoetoxi)quinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxi-7-(2-morfolinoetoxi)quinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxi-7-(3-morfolinopropoxi)quinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxi-7-[2-(4-prop-2-inilpiperazin-1-il)etoxi]quinazolina,
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-5-isopropoxi-7-[2-(4-metilpiperazin-1-il)etoxi]quinazolina y
4-(5-cloro-2,3-metilendioxipirid-4-ilamino)-7-{2-[4-(2-dimetilaminoacetil)piperazin-1-il]etoxi}-5-isopropoxiquinazolina;
o su sal de adición de ácido farmacéuticamente aceptable.

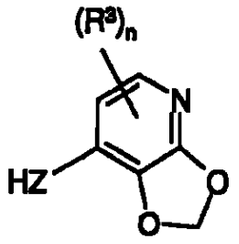
18. Un proceso para la preparación de un derivado de quinazolina de la Fórmula I, o su sal farmacéuticamente aceptable, de acuerdo con la reivindicación 1 que comprende:-

(a) para la producción de aquellos compuestos de la Fórmula I en donde Z es un grupo O, S o N(R^2), la reacción de una quinazolina de la Fórmula II



II

en donde L es un grupo desplazable y m y R^1 tienen cualquiera de los significados definidos anteriormente, excepto que cualquier grupo funcional se protege, si es necesario, con un compuesto de la Fórmula III



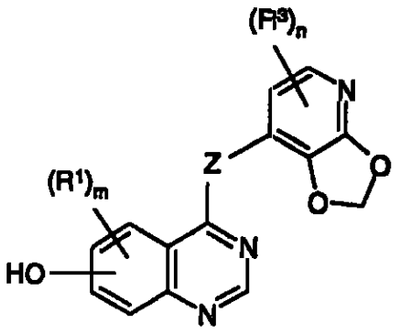
III

en donde Z es O, S, o N(R^2) y n, R^3 y R^2 tienen cualquiera de los significados definidos anteriormente, excepto que cualquier grupo funcional se protege, si es necesario, tras lo cual cualquier grupo protector, que esté presente, se retira por medios convencionales.

(b) para la producción de aquellos compuestos de la Fórmula I en donde por lo menos un grupo R^1 es un grupo de la fórmula

$$Q^1 - X^1-$$

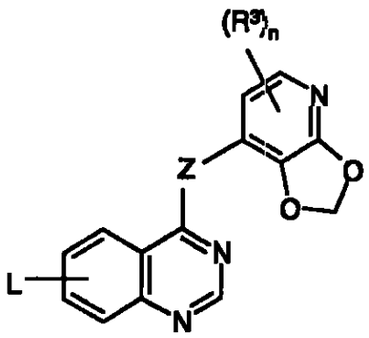
en donde Q^1 es un grupo aril-(1-6C)alquilo, (3-7C)cicloalquil-(1-6C)alquilo, (3-7C)cicloalquenil-(1-6C)alquilo, heteroarilo:(1-6C)alquilo o heterociclil-(1-6C)alquilo o un grupo alquilo sustituido opcionalmente y X^1 es un átomo de oxígeno, el acoplamiento, convenientemente en la presencia de un agente deshidratante apropiado, de una quinazolina de la Fórmula V



V

en donde m, R^1, Z, n y R^3 tienen cualquiera de los significados definidos anteriormente, excepto que cualquier grupo funcional se protege, si es necesario, con un alcohol apropiado, tras lo cual cualquier grupo protector, que esté presente, se retira por medios convencionales.

(c) para la producción de aquellos compuestos de la Fórmula I en donde un grupo R^1 contiene un grupo (1-6C)alcoxi o (1-6C)alcoxi sustituido o un grupo (1-6C)alquilamino o (1-6C)alquilamino sustituido, la reacción de un derivado de quinazolina de la Fórmula VI



VI

en donde L es un grupo desplazable, como se define anteriormente, y Z, n y R^3 tienen cualquiera de los significados definidos en la reivindicación 1, excepto que cualquier grupo funcional se protege, si es necesario, con un alcohol o amina, según lo apropiado, tras lo cual cualquier grupo protector, que esté presente, se retira por medios convencionales.

(d) para la producción de aquellos compuestos de la Fórmula I en donde R^1 es un grupo (1-6C)alcoxi amino-sustituido, la reacción de un compuesto de la Fórmula I en donde R^1 es un grupo (1-6C)alcoxi halógeno-sustituido con un compuesto heterociclilo que contiene nitrógeno o una amina apropiada.

(e) Para la producción de aquellos compuestos de la Fórmula I en donde R^1 es un grupo (1-6C)alcoxi amino-hidroxi-disustituido, la reacción de un compuesto de la Fórmula I en donde el grupo R^1 contiene un grupo (1-6C)alcoxi epoxi-sustituido con un compuesto heterociclilo o una amina apropiada.

(f) para la producción de aquellos compuestos de la Fórmula I en donde Z es un grupo SO ó SO_2, la oxidación de un compuesto de Fórmula I en donde Z es un grupo S.

(g) para la producción de aquellos compuestos de la Fórmula I en donde un grupo R^1 contiene un grupo heterocíclico N-acilado, la acilación de un derivado de quinazolina de la Fórmula I en donde el grupo R^1 contiene un grupo heterocíclico con un grupo NH no sustituido.

y cuando se requiere una sal farmacéuticamente aceptable, un derivado de quinazolina de la Fórmula I puede obtenerse por la reacción de dicho derivado de quinazolina con un ácido adecuado usando un procedimiento convencional.

19. Una composición farmacéutica que comprende un derivado de quinazolina de la Fórmula I, o su sal farmacéuticamente aceptable, de acuerdo con la reivindicación 1, en asociación con un diluyente o vehículo farmacéuticamente aceptable.

20. Un derivado de quinazolina de la Fórmula I, o su sal farmacéuticamente aceptable, de acuerdo con la reivindicación 1, para uso en un método de tratamiento del cuerpo animal o humano mediante terapia.

21. El uso de un derivado de quinazolina de la Fórmula I, o su sal farmacéuticamente aceptable, de acuerdo con la reivindicación 1, en la manufactura de un medicamento para uso como agente anti-invasivo en la contención y/o tratamiento de enfermedad de tumor sólido.

22. Un método para producir un efecto anti-invasivo por la contención

y/o tratamiento de enfermedad de tumor sólido en un animal de sangre caliente necesitado de tal tratamiento. que comprende administrar a dicho animal una cantidad efectiva de un derivado de quinazolina de la Fórmula I, o su sal farmacéuticamente aceptable, de acuerdo con la reivindicación 1.

AS 96866

PATENT COOPERATION TREATY

PCT

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To.

ASTRAZENECA
Global Intellectual Property
S-151 85 Södertälje
SUEDE

CODE	DATE	NTD

ARKOM 18.OCT.2004 GIPS

DATA ENTERED

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

29 OCT 2004

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	14/10/2004

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
100878-1 WO	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB03/04703	29/10/2003	04/11/2002

Applicant

ASTRAZENECA AB et al.

1 The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3 Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)) Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx 523656 epmu d Fax. (+49-89) 2399-4465	FERRO VASCONCELOS M Tel. (+49-89) 2399 2828

Europäisches Patentamt · European Patent Office · Office européen des brevets

Form PCT/IPEA/416 (August 2002) P20473

CODE	DATE	NTD

ANKOM 18. OCT. 2004 GIPS

DATA ENTERED

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
100878-1 WO		
International application No	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB03/04703	29/10/2003	04/11/2002
International Patent Classification (IPC) or national classification and IPC		
C07D491/04		
Applicant		
ASTRAZENECA AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 2 sheets, including this cover sheet

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25/05/2004	11/10/2004
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax (+49-89) 2399-4465	TZSCHOPPE D A Tel (+49-89) 2399 2828

Europäisches Patentamt · European Patent Office · Office européen des brevets

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT); see also international search report)

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out.

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

PCT/GB2003/004703

PATENT COOPERATION TREATY

cc. RTI

216 BST

PCT

From the INTERNATIONAL BUREAU

To:

TAIT, Brian, Steele
ASTRAZENECA_AB
Global Intellectual Property
SE-151 85 Södertälje
Sweden

CODE	DATE	NTD

ANKOM 18 OCT 2004 GPS

ENTERED CLERK

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year)
11 October 2004 (11.10.2004) 15 NOV 2004

Applicant's or agent's file reference
100878-1 WO

International application No.
PCT/GB2003/004703

IMPORTANT NOTIFICATION

International filing date (day/month/year)
29 October 2003 (29.10.2003)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address
TAIT, Brian, Steele
ASTRAZENECA
Global Intellectual Property
P O Box 272
Mereside
Macclesfield, Cheshire SK10 4GR
United Kingdom

State of Nationality

State of Residence

Telephone No
+44 1625 230148

Facsimile No
+44 1625 510752

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
TAIT, Brian, Steele
ASTRAZENECA AB
Global Intellectual Property
SE-151 85 Sodertalje
Sweden

State of Nationality

State of Residence

Telephone No.
+46 8 553 260 00

Facsimile No.
+44 8 553 288 20

Teleprinter No

3. Further observations, if necessary:
Change in agent's address.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.87 40

Authorized officer
Paulette BOCCARD

Telephone No (41-22) 338 8147

PCT REQUEST

100878-1 WO

Duplicate of original printed on 21 10 2003 03 04 07 PM

0	**For receiving Office use only**	
0-1	International Application No	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	

0-4	**Form - PCT/RO/101 PCT Request**	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.11.2003)
0-5	**Petition** The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	**Receiving Office (specified by the applicant)**	United Kingdom Patent Office (RO/GB)
0-7	**Applicant's or agent's file reference**	100878-1 WO
I	**Title of invention**	QUINAZOLINE DERIVATIVES
II	**Applicant**	
II-1	This person is	applicant only
II-2	Applicant for	AP: (GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW); EA: (AM AZ BY KG KZ MD RU TJ TM); EP: (AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR); OA: (BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG); AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI 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 MK MN MW MX MZ 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 UZ VC VN YU ZA ZM ZW
II-4	Name	ASTRAZENECA AB
II-5	Address	Sodertalje S-151 85 Sweden
II-6	State of nationality	SE
II-7	State of residence	SE
II-8	Telephone No	+44 1625 230148
II-9	Facsimile No	+44 1625 510752

PCT REQUEST

100878-1 WO

Duplicate of original printed on 21 10 2003 03.04.07 PM

III-1	**Applicant and/or Inventor**	
III-1-1	This person is	applicant only
III-1-2	Applicant for	MG
III-1-4	Name	ASTRAZENECA UK LIMITED
III-1-5	Address	15 Stanhope Gate London, Greater London W1K 1LN United Kingdom
III-1-6	State of nationality	GB
III-1-7	State of residence	GB
III-2	**Applicant and/or Inventor**	
III-2-1	This person is	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	PLE, Patrick
III-2-5	Address	AstraZeneca Pharma Z.I. La Pompelle BP 1050 F-51689 Reims Cedex 2 France
III-2-6	State of nationality	FR
III-2-7	State of residence	FR
IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as.	agent:
IV-1-1	Name (LAST, First)	TAIT, Brian, Steele
IV-1-2	Address	ASTRAZENECA Global Intellectual Property P O Box 272 Mereside Alderley Park Macclesfield, Cheshire SK10 4GR United Kingdom
IV-1-3	Telephone No	+44 1625 230148
IV-1-4	Facsimile No	+44 1625 510752

PCT REQUEST

100878-1 WO

Duplicate of original printed on 21 10 2003 03 04 07 PM

V	**Designation of States**	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	**AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT** **EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT** **EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT** **OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT**
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	**AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI 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 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**
V-5	**Precautionary Designation Statement** In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4 9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit	
V-6	**Exclusion(s) from precautionary designations**	**NONE**
VI-1	**Priority claim of earlier regional application**	
VI-1-1	Filing date	**04 November 2002 (04.11.2002)**
VI-1-2	Number	**02292736.2**
VI-1-3	Regional Office	**EP**

220

PCT REQUEST 100878-1 WO

Duplicate of original printed on 21 10 2003 03 04 07 PM

VI-2	**Priority claim of earlier regional application**		
VI-2-1	Filing date	10 April 2003 (10.04.2003)	
VI-2-2	Number	03290900.4	
VI-2-3	Regional Office	EP	
VII-1	**International Searching Authority Chosen**	European Patent Office (EPO) (ISA/EP)	
VIII	**Declarations**	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	**Check list**	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	-
IX-2	Description	100	-
IX-3	Claims	20	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	126	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-19	**Figure of the drawings which should accompany the abstract**		
IX-20	**Language of filing of the international application**	English	
X-1	**Signature of applicant, agent or common representative**		
X-1-1	Name (LAST, First)	TAIT, Brian, Steele	

FOR RECEIVING OFFICE USE ONLY

10-1	**Date of actual receipt of the purported international application**	
10-2	**Drawings**	
10-2-1	Received	
10-2-2	Not received	

PCT REQUEST 100878-1 WO

Duplicate of original printed on 21 10 2003 03 04 07 PM

10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

222

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EPO

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: 100878-1 WO

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/GB03/04703	29 October 2003 (29.10.2003)	04 November 2002 (04.11.2002)

Title of invention: QUINAZOLINE DERIVATIVES AS SRC TYROSINE KINASE INHIBITORS

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country)*

ASTRAZENECA AB
SE-151 85 Sodertalje
Sweden

Telephone No.: +46 8 553 26000
Facsimile No.: +46 8 553 28820
Teleprinter No:
Applicant's registration No. with the Office:

State *(that is, country)* of nationality: SE

State *(that is, country)* of residence: SE

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country)*

ASTRAZENECA UK LIMITED
15 Stanhope Gate
London
W1K 1LN
United Kingdom

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

Name and address: *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country)*

PLE, Patrick
AstraZeneca Pharma
Z.I. La Pompelle BP 1050
51689 Reims Cedex 2
France

State *(that is, country)* of nationality: FR

State *(that is, country)* of residence: FR

☐ Further applicants are indicated on a continuation sheet.

International application No
PCT/GB03/04703

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative

and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country)*

Agent
ASTRAZENECA
Global Intellectual Property
SE-151 85 Sodertalje
Sweden

Telephone No
+246 8 553 26000
Facsimile No
+46 8 553 28820
Teleprinter No.

Agent's registration No with the Office

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description ☒ as originally filed
☐ as amended under Article 34

the claims ☒ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings ☐ as originally filed
☐ as amended under Article 34

2 ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3 ☐ The applicant wishes the start of the international preliminary examination to be **postponed** until the expiration of the applicable time limit under Rule 69.1(d)

4 ☐ The applicant expressly wishes the international preliminary examination to **start earlier** than at the expiration of the applicable time limit under Rule 54*bis* 1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.
☐ which is the language of a translation furnished for the purposes of international search.
☐ which is the language of publication of the international application.
☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

223

CHAPTER II

223

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/GB03/04703	For International Preliminary Examining Authority use only
Applicant's or agent's file reference 100878-1 WO	Date stamp of the IPEA

RECIBIDO
11 ABR 2005
BRIGARD & CASTRO
RECEIVED

Applicant
AstraZeneca AB et al

CALCULATION OF PRESCRIBED FEES

1. Preliminary examination fee	EURO 510.00 P	
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	EURO 129.00 H	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	EURO 639.00 TOTAL	

MODE OF PAYMENT

☒	authorization to charge deposit account with the IPEA (see below)	☐	cash
☐	cheque	☐	revenue stamps
☐	postal money order	☐	coupons
☐	bank draft	☐	other *(specify)*

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all IPEAs)

IPEA/ EPO

☒ Authorization to charge the total fees indicated above.

☒ *(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above

Deposit Account No. 2810.0023

Date 8 A - Dec

Name Shirley Douglas

Signature: _____

See Notes to the fee calculation sheet

International application No.
PCT/GB03/04703

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No IV, for the purposes of international preliminary examination:

			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34		sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	.	sheets	☐	☐
5. letter	.	sheets	☐	☐
6 other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in computer readable form
7. ☐ tables in computer readable form related to a sequence listing
8. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand)

Brian S. Tait

Brian Steele TAIT et al
Global Intellectual Property, Patents, AstraZeneca AB

For International Preliminary Examining Authority use only

1 Date of actual receipt of DEMAND

2 Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b)

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply
   ☐ The applicant has been informed accordingly
4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.
6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54*bis*.1(a) and item 7 or 8, below, does not apply.
7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54*bis*.1(a) as extended by virtue of Rule 80.5.
8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54*bis* 1(a), the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

See Notes to the demand form

95866

224

HORNE ENGALL & FREEMAN
Solicitors Commissioners for Oaths Notaries Public

Kenneth Greenwood - Notary Public
Nicholas D Jamison - Notary Public

Conveyancer
Francois Botha

47A HIGH STREET
EGHAM · SURREY
TW20 9ES
Telephone - 01784 432292

FAX No. 01784-431964 DX 53100 Egham

Our Ref | Your Ref | Date

I, KENNETH GREENWOOD, Notary Public of the Town of Egham in Surrey, duly admitted and sworn, practising in the said Town,

DO HEREBY CERTIFY AND ATTEST:

THAT the signature (Patrick PLE) set and subscribed at the foot of the hereunto annexed document is genuine.

IN TESTIMONY WHEREOF I have hereunto set my hand and affixed my Seal of Office in the Town of Egham aforesaid, this 2nd day of March Two Thousand and Five

NOTARY PUBLIC
MY COMMISSION IS PERMANENT

213220

225

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1 Country United Kingdom of Great Britain and Northern Ireland
Pays Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le present acte public

2 Has been signed by **Kenneth Greenwood**
a ete signe par

3 Acting in the capacity of **Notary Public**
agissant en qualite de

4 Bears the seal/stamp of **The Said Notary Public**
est revêtu du sceau/timbre de

Certified/Attesté
5 at London/a Londres 6 the/le **03 March 2005**

7 by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majeste aux Affaires Etrangeres et du Commonwealth

8 Number/sous No **G637562**

9 Stamp
timbre

10 Signature **A. Bantin**

FOREIGN AND COMMONWEALTH OFFICE LONDON

For the Secretary of State / Pour le Secretaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country An apostille or legalisation certificate only confirms that the signature seal or stamp on the document is genuine It does not mean that the contents of the document are correct or that the Foreign & Commonwealth Office approves of the contents

100878-1P/CO

ASSIGNMENT

The undersigned,

PLE, Patrick

domiciled in

AstraZeneca Pharma, Z I La Pompelle, BP 1050. F-51689 Reims, Cedex 2, France

hereby state under oath to be the sole and true inventor of

QUINAZOLINE DERIVATIVES AS SRC TYROSINE KINASE INHIBITORS

Istate as well that I assign, without reservations or limitation, in favor of

AstraZeneca AB

a corporation organized and existing under the laws of

Sweden

domiciled in

SE-151 85 Sodertalje, Sweden

all rights inherent to said invention, and that the above mentioned corporation hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia

TRASPASO

abajo firmado

domiciliado en

declara bajo juramento ser único y verdadero inventor de.

Declara asimismo que cede y transfiere sin reserva ni limitación, a favor de la sociedad

organizada y existente de conformidad con la leyes de

domiciliada en

Todos los derechos inherentes a dicha invención y que la citada sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

Patrick PLE

PLE, Patrick

CERTIFICADO NOTARIAL (INDIVIDUO)

A los 21 días del mes de MARZO 2005, comparecí personalmente ante mi, Notario Publico,

a quien doy fé de conocer y me consta que la persona descrita y firmante del documento que precede, declarado ante mí que otorga el mismo para los fines y propósitos que en él se expresan

NOTARY PUBLIC (Notario Público)

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this day of 2005 personally appeared before me, a Notary Public,

to me known and known to me to be the person described in and who executed the foregoing document, and duly acknowledged to me that executed the same for the uses and purposes therein expressed

CERTIFICADO NOTARIAL (INDIVIDUO)

A los 21 días del mes de MARZO 2005, comparecí personalmente ante mi, Notario Publico, PATRICK PLE

a quien doy fé de conocer y me consta que la persona descrita y firmante del documento que precede, declarado ante mí que otorga el mismo para los fines y propósitos que en él se expresan

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this day of 2005 personally appeared before me, a Notary Public,

to me known and known to me to be the person described in and who executed the foregoing document, and duly acknowledged to me that executed the same for the uses and purposes therein expressed

228

TRADUCCION AL ESPAÑOL del documento de cesión a AstraZeneca AB y firmado por el cedente y el cesionario.

YO, KENNETH GREENWOOD, Notario Público del Pueblo de Egham en Surrey, debidamente admitido y jurado, practicando en dicho pueblo,

CERTIFICO Y ATESTO POR LA PRESENTE·

QUE la firma (Patrick PLE) fijada y suscrita al pie del documento anexo al presente es genuina.

EN TESTIMONIO DE LO CUAL he puesto mi firma y fijado mi Sello de Oficina en el Pueblo de Egham, este 2 de Marzo de dos mil cinco.

(Firma)

NOTARIO PUBLICO
MI COMISION ES PERMANENTE

229

APOSTILLA

(Convención de La Haya del 5 de Octubre de 1961)

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
   Este documento público
2. Ha sido firmado por **Kenneth Greenwood**
3. Actuando en capacidad de **Notario Público**
4 Lleva el sello/timbre de **Dicho Notario Público**

Certificado

5. en Londres 6. el **3 de Marzo de 2005**

7 por el Secretario Principal de Su Majestad de Relaciones Exteriores y de la Mancomunidad.

8 Número **G637562**

9. Sello 10 Firma **A. Bantin**
   (Firma)

Por el Secretario de Estado

Si este documento ha de usarse en un país que no es parte del Convenio de La Haya del 5 de Octubre de 1961, debe ser presentado a la sección consular de la misión que representa a ese país. Una apostilla o certificado de legislación solo confirma que la firma, sello o timbre en el documento son genuinos No significa que el contenido del documento sea correcto o que la Oficina Exterior y de la Comunidad apruebe su contenido

Brigard & Castro

BOGOTA - COLOMBIA

230

PODER

Yo (nosotros)

domiciliado(s) en

Nombro(amos) a: **RAMIRO CASTRO DUQUE** y/o **JUAN PABLO CADENA SARMIENTO** y/o **BEATRIZ JARAMILLO S.**
de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como oposiciones al registro de marcas, acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros) intereses), con todas las demás facultades legales necesarias

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, conciliar la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: **RAMIRO CASTRO DUQUE** y/o **JUAN PABLO CADENA SARMIENTO** y/o **BEATRIZ JARAMILLO S.**
domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

Otorgado y firmado en

hoy de de 200_

Firma

Nombre

Cargo

POWER OF ATTORNEY

I (We) ASTRAZENECA AB

domiciled in SE-151-Sodertalje, Sweden

Hereby appoint **RAMIRO CASTRO DUQUE** and/or **JUAN PABLO CADENA SARMIENTO** and/or **BEATRIZ JARAMILLO S.**
of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models, registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as. oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or explotation of licenses, action of unfair competition, penal demands, actions of indemnities for damages: claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures: and in other actions or similar proceedings.

To that effect they are hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kind of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions At the same time I (We) hereby appoint **RAMIRO CASTRO DUQUE** and/or **JUAN PABLO CADENA SARMIENTO** and/or **BEATRIZ JARAMILLO S.**
domiciled in Carrera 7 No. 16-56, Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys

Granted and Signed in Macclesfield, Cheshire, England

this 18th day of July 2003

Signature

Name KEVIN BILL

27 ENE. 2005

NOTARIO CUARENTA (E)

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy de de
personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el anterior documento, debidamente juramentado declaró y dijo que él es

de

Sociedad legalmente constituida para un período de duración que aún no ha terminado, que el declarante está autorizado por dicha compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y representación de la expresada compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad.

Estado de
con fecha

y que quien confiere el presente poder es su representante.

Notario Público (sello)

NOTARIAL CERTIFICATE (CORPORATION)

On this 18th day of July 2003
personally appeared before me
KEVIN BILL
to me known, and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the
ATTORNEY
of
ASTRAZENECA AB

Which is legally constituted for a term not yet expired, that deponent is authorized by said Company to confer this Power of Attorney; that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof, and that purpose for which this instrument is granted included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company.

State of Sweden
under date of 1st January 2003

and that he (she) who grants the present power of attorney is its Representative.

Notary Public (Seal)

CERTIFICADO NOTARIAL PERSONA NATURAL

Hoy de de , compareció(eron)
ante mí

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él se expresan.

Notario Público (sello)

En la Notaría Cuarenta de este Círculo se cotejó la presente fotocopia que corresponde al original que se ha tenido a la vista
27 ENE. 2005
NOTARIO CUARENTA (E)
Luis Alexander Arias Betancourt
Bogotá, D.C., Colombia

NOTARIAL CERTIFICATE NATURAL PERSON

On this day of of
personally appeared before me

who is(are) known to me and who I attest executed the foregoing document and he (they) declared he (they) grant(s) the document for the uses and purposes therein expressed.

Notary Public (Seal)

LEGALIZACION POR APOSTILLA ES REQUERIDA.

LEGALIZATION BY APOSTILLE IS REQUIRED.

231

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1 Country United Kingdom of Great Britain and Northern Ireland
Pays Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le present acte public

2 Has been signed by **J B Hodgson**
a ete signé par

3 Acting in the capacity of **Notary Public**
agissant en qualité de

4 Bears the seal/stamp of **The Said Notary Public**
est revêtu du sceau/timbre de

Certified/Attesté

5 at London/à Londres 6 the/le **17 February 2004**

7 by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majeste aux Affaires Etrangères et du Commonwealth

8 Number/sous No **G348987**

9 Stamp
timbre

10 Signature **J. Ireland**

FOREIGN AND COMMONWEALTH OFFICE LONDON

En la Notaría Cuarenta de este Círculo se cotejó la presente fotocopia que coincide con el original que se ha tenido a la vista
27 ENE. 2005
NOTARIO CUARENTA
Luis Alexander Arias Betancourt
Bogotá, D.C., Colombia

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961,
it should be presented to the consular section of the mission representing that country.

230 232

TRADUCCIÓN SIMPLE AL ESPAÑOL del la Apostilla que vienen junto con el Certificado Notarial (Sociedad) y el **Poder** concedido por **ASTRAZENECA AB**, domiciliada en SE - 151 Sodertalje, Suecia a **Ramiro Castro Duque** y/o **Juan Pablo Cadena Sarmiento** y/o **Beatriz Jaramillo S**, domiciliados en la Carrera 7 #16-56, P 9, Bogotá D C , Colombia

AUTENTICACIÓN

(Convención de La Haya del 5 de Octubre de 1961)

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1 País: Reino Unido de Gran Bretaña e Irlanda del Norte

2 Este documento público ha sido firmado por **J. B. Hodgson**

3 actuando en capacidad de **Notario Público**

4 lleva el sello de. **Dicho Notario Público**

CERTIFICADO

5 en Londres 6 el **17 de Febrero de 2004**

7 por El secretario de Estado Principal de Su Majestad para Asuntos Exteriores y de la Comunidad

8 No **G348987**

9 Sello 10 Firma

J. Ireland (Firma)

En la Notaría Cuarenta de este Círculo se cotejó la presente fotocopia que coincide con el original que se ha tenido a la vista
27 ENE. 2005
NOTARIO CUARENTA (E)
Luis Alexander Arias Betancourt
Bogotá, D.C. Colombia

Si este documento va a ser utilizado en un país que no es parte de la Convención de la Haya del 5 de Octubre de 1961, debe ser presentado a la sección consular de la misión que representa a ese país

REPÚBLICA DE COLOMBIA

233

GAVIRI A

ORGANIZACION ELECTORAL
REGISTRADURÍA NACIONAL DEL ESTADO CIVIL

REGISTRO CIVIL DE DEFUNCIÓN

Indicativo Serial 5562241

Datos de la oficina de registro

Clase de oficina: Registraduría [ ] Notaría [X] Consulado [ ] Corregimiento [ ] Insp. de Policía [ ] Código 9795

País - Departamento - Municipio - Corregimiento e/o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D..C NOTARIA 32.

Datos del inscrito

Apellidos y nombres completos

CASTRO DUQUE RAMIRO

Documento de identificación (Clase y número)	Sexo (en Letras)
C.C. No. 170322 DE BOGOTA ------------	MASCULINO

Datos de la defunción

Lugar de la Defunción: País - Departamento - Municipio - Corregimiento e/o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D.C.

Fecha de la defunción	Hora	Número de certificado de defunción
Año 2004 Mes 10 Día 30	04:10 PM	A- 2094375.

Presunción de muerte

Juzgado que profiere la sentencia	Fecha de la sentencia
-------------------	Año Mes Día

Documento presentado	Nombre y cargo del funcionario
Autorización judicial [ ] Certificado Médico [X]	ANDRES DIAZ CAMPOS.- R.M. No. 79982662

Datos del denunciante

Apellidos y nombres completos

EDGAR DAVID REGINO H.

Documentos de identificación (Clase y numero)	Firma
C.C.No. 15.030.154 DE LORICA/ CORDOBA	[firma]

Primer testigo

Apellidos y nombres completos

Documentos de identificación (Clase y número)	Firma
------------------	------------

Segundo testigo

Apellidos y nombres completos

Documentos de identificación (Clase y numero)	Firma
------------------	------------

Fecha de inscripción	Nombre y firma del funcionario que autoriza
Año 2004 Mes 11 Día 02	BLANCA LUCIA ... RESTREPO NOTARIA ...

ESPACIO PARA NOTAS

PADRES: ALFONSO CASTRO
MERCEDES DUQUE.

ORIGINAL PARA LA OFICINA DE REGISTRO

NOTARIA 32
DEL CIRCULO DE SANTA FE DE BOGOTA, D.C.

Germán Eleázar Moreno L.
Notario

COMO SECRETARIO DELEGADO DE LA NOTARIA TREINTA Y DOS (32) DEL CIRCULO DE BOGOTA

CERTIFICO QUE:

La presente acta es fiel copia del original tomada del registro civil de defunciones serial indicativo número: ST6220[illegible]

que expido en la ciudad de Bogotá D.C., hoy: 05 NOV. 2004

NELSON FLOREZ C.
SECRETARIO DELEGADO

SUPERINDUSTRIA Y COMERCIO
Radicacion 05042313 00000000 Folios 231
Fecha (AMD) 2005-05-03 16 59 02
Tramite 811 PCT PATENT 379 FASE NACI 411 PRESENTA
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓ MODELO DE UTILIDAD	( )	(✓)
Indicacion de que se solicita la concesion de una patente ✓	( )	(✓)
Datos de identificacion del solicitante o de la persona que se presenta la solicitud	(✓)	(✓)
Descripcion de la Invencion	( )	(✓)
Dibujos de ser estos pertinentes ✕	( )	(✓)
Comprobante de Pago de las tasas establecidas		
COMPLETA ( ) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicacion de que se solicita el registro de Diseño Industrial	(✓)	(✓)
- Datos de identificación del solicitante o de la persona que presenta	( )	(✓)
- la solicitud		
- Representación grafica o fotografica del Diseño Industrial o muestra del Material que incorpora el diseño	( )	(✓)
Comprobante de pago de las tasas establecidas	(✓)	(✓)
COMPLETA ( ) INCOMPLETA	(✓)	( )
ESQUEMA DE TRAZADO ( )		
- Indicacion de que solicita el registro de un Esquema de trazado	( )	(✓)
- Datos de identificación del solicitante o de la persona que presenta La solicitud	( )	( )
Representacion grafica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable Claudia M Neva

Fecha

235

Industria y Comercio
SUPERINTENDENCIA

Folio 233

2020
Bogotá DC

Doctor(a)
JUAN PABLO CADENA SARMIENTO
Apoderado(a)
ASTRAZENECA AB

REFERENCIA:	Radicación No.	05 42313
	Solicitud Internacional	PCT/GB2003/004703
	Fecha límite inicio fase Nacional	04 – 06 - 2005
	Trámite	011
	Evento	379
	Actuación	416
	Oficio No	521
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC 28 JUL. 2005

ALIX CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

Al contestar favor indique el número de radicacion consignado en el sticker

Sede Centro Carrera 13 No 27-00 Pisos 2 5, 7 y 10
Conmutador 3 820840 Fax 3 505220
Sede CAN Tr 40A No 38-50 3153265 al 69
Fax 3 505220 Linea 9800-910 165
Web www.sic.gov.co e-mail info@sic.gov.co
Bogotá D C - Colombia