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SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

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54 **TITULO** IMIDAZOLO-5-IL-'-ANILINOPIRIMIDINAS COMO AGENTES PARA LA INHIBICION DE LA PROLIFERACION CELULAR

51 **CLASIFICACION INTERNACIONAL**

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1 SOLICITUD DE.

☒ Patente de Invención ☐ Patente de Modelo de Utilidad

☒ Capítulo I ☐ Capítulo II

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10 **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud $463.000
- [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)
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- [ ] Traducción del examen preliminar efectuado por la IPEA.
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- [ ] 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.
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11 **FIGURA CARACTERÍSTICA.**

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FIRMA.

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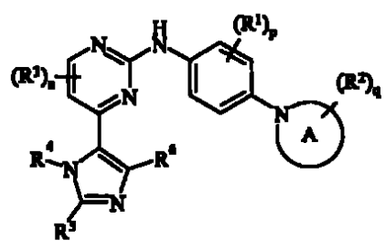
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(54) Title: IMIDAZOLO-5-YL-2-ANILINOPYRIMIDINES AS AGENTS FOR THE INHIBITION OF CELL PROLIFERATION



(I)

(57) Abstract: Compounds of the formula (I), wherein variable groups are as defined within and a pharmaceutically acceptable salts and in vivo hydrolysable esters are described. Also described are processes for their preparation and their use as medicaments, particularly medicaments for producing a cell cycle inhibitory (anti cell proliferation) effect in a warm blooded animal, such as man.

WO 2005/075461 A1

CHEMICAL COMPOUNDS

The invention relates to pyrimidine derivatives, or pharmaceutically acceptable salts or *in vivo* hydrolysable esters thereof, which possess cell-cycle inhibitory activity and are accordingly useful for their anti-cell-proliferation (such as anti-cancer) activity and are therefore useful in methods of treatment of the human or animal body The invention also relates to processes for the manufacture of said pyrimidine derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments of use in the production of an anti-cell proliferation effect in a warm-blooded animal such as man.

The cell cycle is fundamental to the survival, regulation and proliferation of cells and is highly regulated to ensure that each step progresses in a timely and orderly manner The progression of cells through the cell cycle arises from the sequential activation and de-activation of several members of the cyclin-dependent kinase (CDK) family The activation of CDKs is dependent on their interaction with a family of intracellular proteins called cyclins Cyclins bind to CDKs and this association is essential for CDK activity (such as CDK1, CDK2, CDK4 and/or CDK6) within the cell Different cyclins are expressed and degraded at different points in the cell cycle to ensure that activation and inactivation of CDKs occurs in the correct order for progression through the cell cycle.

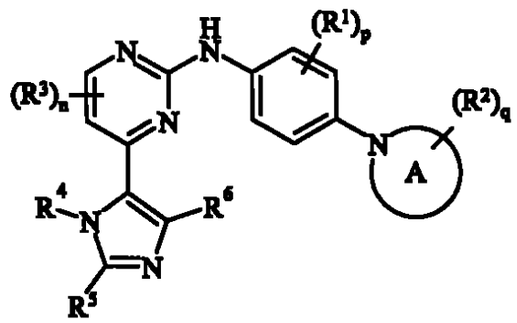
Moreover, CDKs appear to be downstream of a number of oncogene signalling pathways. Deregulation of CDK activity by upregulation of cyclins and/or deletion of endogenous inhibitors appears to be an important axis between mitogenic signalling pathways and proliferation of tumour cells

Accordingly it has been recognised that an inhibitor of cell cycle kinases, particularly inhibitors of CDK1, CDK2 and/or CDK4 (which operate at the G2/M, G1/S-S-G2/M and G1-S phases respectively) should be of value as an active inhibitor of cell proliferation, such as growth of mammalian cancer cells

The inhibition of cell cycle kinases is expected to be of value in the treatment of disease states associated with aberrant cell cycles and cell proliferation such as cancers (solid tumours and leukemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

WO 02/20512, WO 03/076435 WO 03/076436, WO 03/076434 and WO 03/076433 describe certain 2-anilino-4-imidazolylpyrimidine derivatives that inhibit the effect of cell cycle kinases. The present invention is based on the discovery that a novel group of 2-(4-heterocyclylanilino)-4-imidazolylpyrimidines surprisingly inhibit the effects of cell cycle kinases showing activity against CDK1 and CDK2, particularly CDK2, and thus possess anti-cell-proliferation properties. The compounds of the present invention are not specifically disclosed in any of the above applications and we have surprisingly found that these compounds possess beneficial properties in terms of one or more of their pharmacological activity (particularly as compounds which inhibit CDK2) and / or pharmacokinetic, efficacious, metabolic and toxicological profiles that make them particularly suitable for *in vivo* administration to a warm blooded animal, such as man. In particular these compounds show improved physical and metabolic properties compared to those previously disclosed.

Accordingly, the present invention provides a compound of formula (I)



(I)

wherein

Ring A is a nitrogen linked 4-7 membered saturated ring which optionally contains an additional nitrogen, oxygen or sulphur atom, wherein if Ring A contains an additional nitrogen atom that nitrogen may be optionally substituted by R^7,

R^1 is halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl or C_{2-6}alkynyl,

p is 0-4, wherein the values of R^1 may be the same or different;

R^2 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, azido, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, carbocyclyl R^{34}-, heterocyclyl-R^{35}-, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl or

N,N-(C_{1-6}alkyl)$_2$sulphamoyl wherein R^2 independently may be optionally substituted on carbon by one or more R^8, or R^2 is NHR^9 -NR^{10}R^{11} or -O R^{12},

q is 0-2, wherein the values of R^2 maybe the same or different,

R^3 is halo nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-3}alkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{1-3}alkoxy, C_{1-3}alkanoyl, *N*-(C_{1-3}alkyl)amino, *N N*-(C_{1-3}alkyl)$_2$amino, C_{1-3}alkanoylamino, *N*-(C_{1-3}alkyl)carbamoyl, *N,N*-(C_{1-3}alkyl)$_2$carbamoyl, C_{1-3}alkylS(O)$_a$ wherein a is 0 to 2, *N* (C_{1-3}alkyl)sulphamoyl or *N N*-(C_{1-3}alkyl)$_2$sulphamoyl, wherein R^3 may be independently optionally substituted on carbon by one or more R^{13},

n is 0 to 2, wherein the values of R^3 may be the same or different;

R^4 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or a carbon-linked heterocyclyl, wherein R^4 may be optionally substituted on carbon by one or more R^{14}, and wherein if said heterocyclyl contains an -NH moiety that nitrogen may be optionally substituted by a group selected from R^{15},

R^5 and R^6 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N N* (C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{3-8}cycloalkyl or a 4-7 membered saturated heterocyclic group, wherein R^5 and R^6 independently of each other may be optionally substituted on carbon by one or more R^{16}, and wherein if a 4-7 membered saturated heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17},

R^7, R^9, R^{10}, R^{11} and R^{12} are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{2-6}alkenylsulphonyl, C_{2-6}alkynylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N N*-(C_{1-6}alkyl)carbamoyl, carbocyclyl, heterocyclyl, carbocyclyl-R^{18}- or heterocyclyl-R^{19}-, wherein R^7, R^9, R^{10}, R^{11} and R^{12} may be independently optionally substituted on carbon by a group selected from R^{20}, and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by R^{21},

R^{14} and R^{20} are independently selected from halo, nitro, cyano hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxyC_{1-6}alkoxy,

C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{1-6}alkyl-R^{22}-, heterocyclylC_{1-6}alkyl-R^{23}-, carbocyclyl-R^{24}- or heterocyclyl-R^{25}-, wherein R^{14} and R^{20} may be independently optionally substituted on carbon by one or more R^{26}, and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{27},

R^{18}, R^{19}, R^{22}, R^{23}, R^{24}, R^{25}, R^{34} or R^{35} are independently selected from -O-, -N(R^{28})-, -C(O)-, -N(R^{29})C(O)-, -C(O)N(R^{30})-, -S(O)$_s$-, -SO_2N(R^{31})- or N(R^{32})SO_2 , wherein R^{28}, R^{29}, R^{30}, R^{31} and R^{32} are independently selected from hydrogen or C_{1-6}alkyl and s is 0-2,

R^{15}, R^{17}, R^{21} and R^{27} and are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl, wherein R^{15}, R^{17}, R^{21} and R^{27} independently of each other may be optionally substituted on carbon by on or more R^{33}, and

R^{8}, R^{13}, R^{16}, R^{26} and R^{33} are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino *N*-methyl-*N*-ethylamino, acetylamino, *N* methylcarbamoyl, *N*-ethylcarbamoyl, *N N*-dimethylcarbamoyl, *N N*-diethylcarbamoyl, *N*-methyl *N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N* methylsulphamoyl, *N*-ethylsulphamoyl, *N N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl,

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

According to a further aspect of the invention there is provided a compound of formula (I) (as depicted above) wherein

Ring A is a nitrogen linked 4-7 membered saturated ring which optionally contains an additional nitrogen, oxygen or sulphur atom, wherein if Ring A contains an additional nitrogen atom that nitrogen may be optionally substituted by R^{7},

R^{1} is halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl or C_{2-6}alkynyl,

p is 0-4, wherein the values of R^{1} may be the same or different,

R^2 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl or *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, wherein R^2 independently may be optionally substituted on carbon by one or more R^8, or R^2 is NHR^9, $-NR^{10}R^{11}$ or $-O-R^{12}$,

q is 0-2, wherein the values of R^2 maybe the same or different;

R^3 is halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-3}alkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{1-3}alkoxy, C_{1-3}alkanoyl, *N*-(C_{1-3}alkyl)amino, *N,N*-(C_{1-3}alkyl)$_2$amino, C_{1-3}alkanoylamino, *N*-(C_{1-3}alkyl)carbamoyl, *N,N*-(C_{1-3}alkyl)$_2$carbamoyl, C_{1-3}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-3}alkyl)sulphamoyl or *N,N*-(C_{1-3}alkyl)$_2$sulphamoyl, wherein R^3 may be independently optionally substituted on carbon by one or more R^{13},

n is 0 to 2, wherein the values of R^3 may be the same or different,

R^4 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or a carbon-linked heterocyclyl, wherein R^4 may be optionally substituted on carbon by one or more R^{14}, and wherein if said heterocyclyl contains an NH- moiety that nitrogen may be optionally substituted by a group selected from R^{15},

R^5 and R^6 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{3-8}cycloalkyl or a 4-7 membered saturated heterocyclic group, wherein R^5 and R^6 independently of each other may be optionally substituted on carbon by one or more R^{16}, and wherein if a 4-7 membered saturated heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17},

R^7, R^9, R^{10}, R^{11} and R^{12} are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{2-6}alkenylsulphonyl, C_{2-6}alkynylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, carbocyclyl, heterocyclyl, carbocyclyl R^{18}- or heterocyclyl-R^{19}- wherein R^7, R^9 R^{10}, R^{11} and R^{12} may be independently

optionally substituted on carbon by a group selected from R^{20}, and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by R^{21},

R^{14} and R^{20} are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{1-6}alkyl-R^{22}-, heterocyclylC_{1-6}alkyl R^{23}-, carbocyclyl-R^{24}- or heterocyclyl-R^{25}-, wherein R^{14} and R^{20} may be optionally substituted on carbon by one or more R^{26}, and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{27},

R^{18}, R^{19}, R^{22}, R^{23}, R^{24}, R^{25} are independently selected from -O-, -N(R^{28})-, -C(O)-, -N(R^{29})C(O)-, C(O)N(R^{30})-, -S(O)$_a$-, -SO_2N(R^{31})- or -N(R^{32})SO_2-, wherein R^{28}, R^{29}, R^{30}, R^{31} and R^{32} are independently selected from hydrogen or C_{1-6}alkyl and a is 0-2,

R^{15}, R^{17}, R^{21} and R^{27} and are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl, wherein R^{15}, R^{17} R^{21} and R^{27} independently of each other may be optionally substituted on carbon by on or more R^{33} and

R^{8}, R^{13}, R^{16}, R^{26} and R^{33} are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N* methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N* methyl *N*-ethylsulphamoyl,

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof

According to a further aspect of the invention there is provided a compound of formula (I) (as depicted above) wherein.

Ring A is a nitrogen linked 4-7 membered saturated ring which optionally contains an additional nitrogen, oxygen or sulphur atom, wherein if Ring A contains an additional nitrogen atom that nitrogen may be optionally substituted by R^7,

R^1 is halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl or C_{2-6}alkynyl,

p is 0-4, wherein the values of R^1 may be the same or different;

R^2 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl or *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, wherein R^2 independently may be optionally substituted on carbon by one or more R^8 or R^2 is -NHR^9, -NR^{10}R^{11} or -O-R^{12},

q is 0-2, wherein the values of R^2 maybe the same or different,

R^3 is halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl C_{1-3}alkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{1-3}alkoxy, C_{1-3}alkanoyl, *N*-(C_{1-3}alkyl)amino, *N,N*-(C_{1-3}alkyl)$_2$amino C_{1-3}alkanoylamino, *N*-(C_{1-3}alkyl)carbamoyl, *N,N*-(C_{1-3}alkyl)$_2$carbamoyl, C_{1-3}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-3}alkyl)sulphamoyl or *N,N*-(C_{1-3}alkyl)$_2$sulphamoyl, wherein R^3 may be independently optionally substituted on carbon by one or more R^{13},

n is 0 to 2, wherein the values of R^3 may be the same or different,

R^4 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or a carbon-linked heterocyclyl, wherein R^4 may be optionally substituted on carbon by one or more R^{14}, and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{15},

R^5 and R^6 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{3-8}cycloalkyl or a 4-7 membered saturated heterocyclic group, wherein R^5 and R^6 independently of each other may be optionally substituted on carbon by one or more R^{16}, and

wherein if a 4-7 membered saturated heterocyclic group contains an -NH moiety that nitrogen may be optionally substituted by a group selected from R^{17},

R^7, R^9, R^{10}, R^{11} and R^{12} are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{2-6}alkenylsulphonyl, C_{2-6}alkynylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, carbocyclyl, heterocyclyl, carbocyclyl R^{18}- or heterocyclyl-R^{19}- wherein R^7, R^9, R^{10}, R^{11} and R^{12} may be independently optionally substituted on carbon by a group selected from R^{20}, and wherein if said heterocyclyl contains an -NH moiety that nitrogen may be optionally substituted by R^{21},

R^{14} and R^{20} are independently selected from halo, nitro cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino carbocyclyl, heterocyclyl, carbocyclylC_{1-6}alkyl-R^{22}-, heterocyclylC_{1-6}alkyl-R^{23} , carbocyclyl-R^{24}- or heterocyclyl-R^{25}-, wherein R^{14} and R^{20} may be optionally substituted on carbon by one or more R^{26}, and wherein if said heterocyclyl contains an -NH moiety that nitrogen may be optionally substituted by a group selected from R^{27}

R^{18}, R^{19} R^{22}, R^{23}, R^{24}, R^{25} are independently selected from -O-, N(R^{28})-, -C(O)-, -N(R^{29})C(O)-, -C(O)N(R^{30})-, -S(O)$_s$-, -SO_2N(R^{31})- or -N(R^{32})SO_2-, wherein R^{28}, R^{29}, R^{30}, R^{31} and R^{32} are independently selected from hydrogen or C_{1-6}alkyl and s is 0-2,

R^{15}, R^{17}, R^{21} and R^{27} and are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl, wherein R^{15}, R^{17}, R^{21} and R^{27} independently of each other may be optionally substituted on carbon by on or more R^{33}, and

R^8, R^{13}, R^{16}, R^{26} and R^{33} are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl,

ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl,

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example, "C_{1-6}alkyl" and "C_{1-4}alkyl" include methyl, ethyl, propyl, isopropyl and *t*-butyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. A similar convention applies to other radicals, for example "carbocyclylC_{1-6}alkyl-R^{20}" includes carbocyclylmethyl-R^{20}, 1-carbocyclylethyl-R^{20} and 2-carbocyclylethyl-R^{20}. The term "halo" refers to fluoro, chloro, bromo and iodo.

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

A "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 4-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, a ring nitrogen atom may optionally bear a C_{1-6}alkyl group and form a quaternary compound or a ring nitrogen and/or sulphur atom may be optionally oxidised to form the *N*-oxide and or the S-oxides. Examples and suitable values of the term "heterocyclyl" are morpholino, piperidyl, pyridyl, pyranyl, pyrrolyl, isothiazolyl, indolyl, quinolyl, thienyl, 1,3-benzodioxolyl, thiadiazolyl, piperazinyl, thiazolidinyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, tetrahydropyranyl, imidazolyl, pyrimidyl, pyrazinyl, pyridazinyl, isoxazolyl, *N*-methylpyrrolyl, 4-pyridone, 1 isoquinolone, 2 pyrrolidone, 4-thiazolidone, pyridine-*N*-oxide and quinoline-*N*-oxide. In one aspect of the invention a "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, it may, unless otherwise specified, be carbon or nitrogen linked, a $-CH_2$ group can optionally be replaced by a -C(O)-and a ring sulphur atom may be optionally oxidised to form the S-oxides.

A "carbocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms, wherein a CH_2- group can optionally be replaced by a

-C(O)- Particularly 'carbocyclyl' is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for 'carbocyclyl' include cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl, naphthyl, tetralinyl, indanyl or 1-oxoindanyl.

A "4-7 membered saturated heterocyclic group" is a saturated monocyclic ring containing 4-7 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a CH_2- group can optionally be replaced by a -C(O)- and a sulphur atom may be optionally oxidised to form the S-oxides. Examples and suitable values of the term "4-7 membered saturated heterocyclic group" are morpholino, piperidyl, 1,4-dioxanyl, 1,3-dioxolanyl, 1,2-oxathiolanyl, imidazolidinyl, pyrazolidinyl, piperazinyl, thiazolidinyl, pyrrolidinyl, thiomorpholino, homopiperazinyl and tetrahydropyranyl.

Ring A is a "nitrogen linked 4-7 membered saturated ring which optionally contains an additional nitrogen, oxygen or sulphur atom". A "nitrogen linked 4-7 membered saturated ring which optionally contains an additional nitrogen, oxygen or sulphur atom" is a saturated monocyclic ring containing 4-7 atoms linked to the phenyl moiety of formula (I) via a nitrogen atom contained in the ring, the ring optionally contains an additional heteroatom selected from nitrogen, sulphur or oxygen, wherein a -CH_2- group can optionally be replaced by a C(O)-, and the optional sulphur atom may be optionally oxidised to form the S-oxides.

Examples of "C_{1-3}alkyl" include methyl, ethyl, propyl and isopropyl. An example of "C_{1-6}alkanoyloxy" is acetoxy. Examples of "C_{1-6}alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C_{1-6}alkoxy" and "C_{1-3}alkoxy" include methoxy, ethoxy and propoxy. Examples of "C_{1-6}alkanoylamino" and "C_{1-3}alkanoylamino" include formamido, acetamido and propionylamino. Examples of "C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2" and "C_{1-3}alkylS(O)$_a$ wherein a is 0 to 2" include methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C_{1-6}alkylS(O)$_r$ wherein r is 1 to 2" include methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C_{1-6}alkanoyl" and "C_{1-3}alkanoyl" include propionyl and acetyl. Examples of "*N*-C_{1-6}alkylamino" and "*N*-C_{1-3}alkylamino" include methylamino and ethylamino. Examples of "*N*,*N*-(C_{1-6}alkyl)$_2$amino" and "*N*,*N*-(C_{1-3}alkyl)$_2$amino" include di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino. Examples of "C_{2-6}alkenyl" and "C_{2-3}alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C_{2-6}alkynyl" and "C_{2-3}alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of '*N*-(C_{1-6}alkyl)sulphamoyl' and

"*N*-(C_{1-3}alkyl)sulphamoyl" are *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$sulphamoyl" and "*N,N*-(C_{1-3}alkyl)$_2$sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of *N*-(C_{1-6}alkyl)carbamoyl" and "*N*-(C_{1-3}alkyl)carbamoyl" are methylaminocarbonyl and ethylaminocarbonyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$carbamoyl" and "*N,N*-(C_{1-3}alkyl)$_2$carbamoyl" are dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of "C_{3-8}cycloalkyl" are cyclopropyl, cyclobutyl, cyclopropyl and cyclohexyl. Examples of "C_{1-6}alkylsulphonylamino" include methylsulphonylamino, isopropylsulphonylamino and *t*-butylsulphonylamino. Examples of "C_{1-6}alkylsulphonyl include methylsulphonyl, isopropylsulphonyl and *t*-butylsulphonyl. Examples of "C_{2-6}alkenylsulphonyl" include vinylsulphonyl, allylsulphonyl and 1 propenylsulphonyl. Examples of "C_{2-6}alkynylsulphonyl" include ethynylsulphonyl, 1-propynylsulphonyl and 2 propynylsulphonyl. Examples of "C_{1-6}alkoxyC_{1-6}alkoxy" include methoxyethoxy, 2-ethoxypropoxy and 2 isopropoxybutoxy. Examples of "C_{1-6}alkoxyC_{1-6}alkoxyC_{1-6}alkoxy" include methoxyethoxymethoxy, 2-ethoxypropoxymethoxy and 3-(2-isopropoxybutoxy)ethoxy. Examples of "C_{2-6}alkenyloxy" include vinyloxy and allyloxy. Examples of "C_{2-6}alkynyloxy" include ethynyloxy and 2-propynyloxy.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

An *in vivo* hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl,

1,3-dioxolen 2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl, and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3 or 4- position of the benzoyl ring

Some compounds of the formula (I) may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers that possess CDK inhibitory activity

The invention relates to any and all tautomeric forms of the compounds of the formula (I) that possess CDK inhibitory activity In particular the skilled reader will appreciate that when R^4 is hydrogen, the imidazole ring as drawn in formula (I) may tautomerise.

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms It is to be understood that the invention encompasses all such solvated forms which possess CDK inhibitory activity

Particular values of variable groups are as follows Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter

Ring A is a nitrogen linked 4-7 membered saturated ring which optionally contains an additional nitrogen or oxygen atom, wherein if Ring A contains an additional nitrogen atom that nitrogen may be optionally substituted by R^7, wherein

R^7 is selected from C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{2-6}alkenylsulphonyl, carbocyclyl-R^{18}- or heterocyclyl-R^{19}-, wherein R^7 may be independently optionally

substituted on carbon by a group selected from R^{20}, and wherein if said heterocyclyl contains an -NH moiety that nitrogen may be optionally substituted by R^{21},

R^{18} and R^{19} are -C(O)-,

R^{20} is selected from halo, cyano, hydroxy, C_{1-6}alkoxy, C_{2-6}alkynyloxy, C_{1-6}alkanoyloxy, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkylS(O)$_a$ wherein a is 2 or heterocyclyl, wherein R^{20} may be optionally substituted on carbon by one or more R^{26},

R^{21} is C_{1-6}alkyl, and

R^{26} is hydroxy

Ring A is a nitrogen linked 4 - 6 membered saturated ring which optionally contains an additional nitrogen or oxygen atom, wherein if Ring A contains an additional nitrogen atom that nitrogen may be optionally substituted by R^7, wherein

R^7 is selected from C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{2-6}alkenylsulphonyl, carbocyclyl R^{18} or heterocyclyl R^{19}-, wherein R^7 may be independently optionally substituted on carbon by a group selected from R^{20}, and wherein if said heterocyclyl contains an -NH moiety that nitrogen may be optionally substituted by R^{21},

R^{18} and R^{19} are -C(O)-,

R^{20} is selected from halo, cyano, hydroxy, C_{1-6}alkoxy, C_{2-6}alkynyloxy, C_{1-6}alkanoyloxy, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkylS(O)$_a$ wherein a is 2 or heterocyclyl, wherein R^{20} may be optionally substituted on carbon by one or more R^{26},

R^{21} is C_{1-6}alkyl, and

R^{26} is hydroxy

Ring A is a nitrogen linked 4-7 membered saturated ring which optionally contains an additional nitrogen, oxygen or sulphur atom, wherein if Ring A contains an additional nitrogen atom that nitrogen may be optionally substituted by R^7, wherein

R^7 is selected from C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{2-6}alkenylsulphonyl, carbocyclyl-R^{18}- or heterocyclyl-R^{19}-, wherein R^7 may be independently optionally substituted on carbon by a group selected from R^{20}, and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by R^{21},

R^{20} is selected from halo, cyano, hydroxy, C_{1-6}alkoxy, C_{2-6}alkynyloxy, C_{1-6}alkanoyloxy, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkylS(O)$_a$ wherein a is 2 or heterocyclyl, wherein R^{20} may be optionally substituted on carbon by one or more R^{26},

R^{18} and R^{19} are -C(O)-,

R^{21} is C_{1-6}alkyl, and

R^{26} is hydroxy

Ring A is a nitrogen linked 6 membered saturated ring which optionally contains an additional nitrogen atom, wherein if Ring A contains an additional nitrogen atom that nitrogen may be optionally substituted by R^7, wherein

R^7 is selected from C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl and C_{2-6}alkenylsulphonyl wherein R^7 may be optionally substituted on carbon by a group selected from R^{20} wherein

R^{20} is selected from hydroxy, C_{1-6}alkoxy, C_{1-6}alkanoyloxy and *N,N*-(C_{1-6}alkyl)$_2$amino

Ring A is piperazin-1-yl, morpholino pyrrolidinyl or azetidinyl, , wherein said piperazin 1-yl may be optionally substituted on nitrogen by R^7, wherein

R^7 is selected from acetyl, propionyl, 2,2-dimethylpropanoyl, 3-methylbutanoyl, butyryl, isobutyryl, mesyl, ethylsulphonyl, ethenylsulphonyl, cyclopropyl-R^{18}-, tetrahydrofuranyl-R^{19}- or pyrrolidinyl-R^{19}- wherein R^7 may be independently optionally substituted on carbon by a group selected from R^{20}, and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by R^{21},

R^{18} and R^{19} are-C(O)-,

R^{20} is selected from fluoro, chloro, cyano, hydroxy, methoxy, prop-2-yn-1-yloxy, acetoxy, dimethylamino, diethylamino, mesyl, tetrazolyl, pyrrolidinyl morpholino, azetidinyl, wherein R^{20} may be optionally substituted on carbon by one or more R^{26},

R^{21} is methyl, and

R^{26} is hydroxy

Ring A is piperazin-1-yl or morpholino, wherein said piperazinyl may be optionally substituted on nitrogen by R^7, wherein

R^7 is selected from acetyl, propionyl, 2-methylpropionyl, 2,2-dimethylpropionyl, butanoyl, 3-methylbutanoyl, mesyl, vinylsulphonyl, cyclopropyl-R^{18}-, pyrrolidin-2-yl-R^{19}-, tetrahydrofuran-2-yl-R^{19}- or tetrahydrofuran-3-yl-R^{19} , wherein R^7 may be independently optionally substituted on carbon by a group selected from R^{20}, and wherein if said heterocyclyl contains an NH- moiety that nitrogen may be optionally substituted by R^{21},

R^{20} is selected from fluoro, chloro, cyano, hydroxy, methoxy, 2-propynyloxy, acetoxy, dimethylamino, diethylamino, mesyl, azetidin 1 yl, pyrrolidin-1 yl, morpholino, tetrazol 1-yl or tetrazol-5-yl, wherein R^{20} may be optionally substituted on carbon by one or more R^{26},

R^{18} and R^{19} are -C(O)-,

R^{21} is methyl, and

R^{26} is hydroxy

Ring A is morpholino or piperazin-1-yl, wherein if Ring A is piperazin-1 yl the -NH- moiety may be optionally substituted by R^7, wherein

R^7 is selected from acetyl, methylsulphonyl, ethylsulphonyl and vinylsulphonyl, wherein R^7 may be optionally substituted on carbon by a group selected from R^{20}, wherein

R^{20} is selected from hydroxy methoxy, acetoxy and dimethylamino

Ring A, R^2 and q together form piperazin-1-yl, morpholino, 4-mesylpiperazin-1-yl, 4-acetylpiperazin-1-yl, 4-(2-acetoxyacetyl)piperazin-1-yl, 4-(2 hydroxyacetyl)piperazin-1-yl, 4-(2-chloroacetyl)piperazin-1-yl, 4-(2-methoxyacetyl)piperazin-1-yl, (3-methoxypropanoyl)piperazin-1-yl (3 hydroxy-3-methylbutanoyl)piperazin-1-yl, (3 hydroxy-2,2-dimethylpropanoyl)piperazin-1-yl, ((R)-3 methyl-2-hydroxybutanoyl)piperazin 1-yl, ((S)-3-methyl-2-hydroxybutanoyl)piperazin-1-yl, 4-(2-dimethylaminoacetyl)piperazin 1-yl, 4-[2-(dimethylamino)ethylsulphonyl]piperazin 1-yl, 4 [2-(methoxy)ethylsulphonyl]piperazin-1-yl, 4-[2-(hydroxy)ethylsulphonyl]piperazin-1-yl, 4-(cyclopropylcarbonyl)piperazin 1-yl, 4-(1-hydroxycyclopropylcarbonyl)piperazin 1-yl, 4-(1-cyanocyclopropylcarbonyl)piperazin-1-yl, 4-(2 hydroxy-2-methylpropanoyl)piperazin-1-yl, 4-((R)-2 hydroxypropanoyl)piperazin-1-yl, 4-((S)-2-hydroxypropanoyl)piperazin 1-yl, 4-((R)-2-methoxypropanoyl)piperazin-1-yl, 4-((S)-2-methoxypropanoyl)piperazin-1-yl, 4-((R)-tetrahydrofuran 2-ylcarbonyl)piperazin-1-yl, 4-((S)-tetrahydrofuran-2 ylcarbonyl)piperazin 1-yl, 4-(isobutyryl)piperazin-1-yl, 4-((R)-2-hydroxybutanoyl)piperazin 1-yl, 4-((S)-2- hydroxybutanoyl)piperazin-1-yl, (R)-3-acetylaminopyrrolidin 1-yl, (S)-3-acetylaminopyrrolidin-1 yl, (R)-2-(cyclopropylaminocarbonyl)pyrrolidin 1-yl, (R)-2-(*N*-methylcarbamoyl)pyrrolidin-1-yl, (S)-2-(*N*,*N*-dimethylcarbamoyl)pyrrolidin-1-yl, 4-(ethenylsulphonyl)piperazin-1-yl, 4-[2-(2-propyn-1-yloxy)acetyl]piperazin 1-yl, 4-(tetrahydrofuran 3-ylcarbonyl)piperazin-1-yl, 4-(3-dimethylaminopropanoyl)piperazin-1-yl, 4-[2-(*N*-methyl-*N* hydroxymethylamino)acetyl]piperazin-1-yl, 4-[3-hydroxy-2-(hydroxymethyl)propanoyl]piperazin-1 yl 4-[2-(1,2,3,4-tetrazol-1-yl)acetyl]piperazin-1-yl, 4-[2-(1,2 3 4-tetrazol-5-yl)acetyl]piperazin-1-yl, 4-(1 methyl-L-prolyl)piperazin 1-yl, 4-[2-(mesyl)acetyl]piperazin-1-yl, 4-(2,2-difluoroacetyl)piperazin-1-yl, 4-[2-(pyrrolidin-1 yl)acetyl]piperazin-1-yl, 4-[2-(morpholino)acetyl]piperazin-1-yl, 4-[2-(diethylamino)acetyl]piperazin-1-yl, 4-(propionyl)piperazin 1-yl, 4-(3-hydroxypropionyl)piperazin-1-yl, 4-[2-(azetidin-1-yl)acetyl]piperazin-1 yl, (R)-3-aminopyrrolidin-1-yl, (S)-3-aminopyrrolidin-1 yl, (3*R*,5*S*)-4-acetyl 3,5-dimethylpiperazin-1-yl, (2*S*,5*R*)-4-acetyl-2,5-dimethylpiperazin-1-yl, (2*RS*,6*SR*)-2,6-dimethylmorpholin-4-

yl]phenyl, 3-hydroxyazetidin-1-yl, 3 acetylaminoazetidin 1-yl, 3-(2-hydroxyacetylamino)azetidin 1-yl, 3-mesylaminoazetidin 1-yl, 3 mesyloxyazetidin-1-yl, 3-azidoazetidin 1-yl, 3-aminoazetidin 1-yl, (3*R*) 3-{[(2*S*)-2-hydroxypropanoyl]amino}pyrrolidin-1-yl, (3*S*)-3-{[(2*S*)-2-hydroxypropanoyl]amino}pyrrolidin-1-yl, (3*S*)-3-(glycoloylamino)pyrrolidin 1-yl and (3*R*)-3-(glycoloylamino)pyrrolidin-1 yl

Ring A is [4-(2-acetoxyacetyl)piperazin-1-yl, [4-(hydroxyacetyl)piperazin-1-yl, 4-((*R*)-2 hydroxybutanoyl)piperazin-1-yl, 4-((R) 2-hydroxypropionyl)piperazin-1-yl, 4-((R)-2-methoxypropionyl)piperazin 1 yl, 4-((R) 3-methyl-2-hydroxybutanoyl)piperazin-1-yl, 4-((*R*)-tetrahydrofur-2-ylcarbonyl)piperazin-1 yl, 4-((*S*)-2-hydroxybutanoyl)piperazin-1-yl, 4-((S)-2 methoxypropionyl)piperazin-1-yl, 4-((*S*)-3-methyl-2-hydroxybutanoyl)piperazin-1 yl, 4-((*S*)-tetrahydrofur-2-ylcarbonyl)piperazin-1-yl, 4-(1-cyanocycloprop-1-ylcarbonyl)piperazin-1-yl, 4-(1-hydroxycycloprop-1-ylcarbonyl)piperazin-1-yl, 4-(1-methyl-L-prolylcarbonyl)piperazin-1-yl, 4-(2-(R)-tetrahydrofur-2 ylcarbonyl)piperazin-1-yl, 4-(2-(S)-2-hydroxypropionyl)piperazin 1-yl)piperazin 1-yl, 4-(2-(S)-tetrahydrofur-2-yl)piperazin-1-yl, 4-(2,2-difluoroacetyl)piperazin-1-yl, 4-(2-acetoxyacetyl)piperazin-1-yl, 4-(2-dimethylaminoacetyl)piperazin 1-yl, 4-(2-dimethylaminoethylsulphonyl)piperazin-1-yl, 4-(2-hydroxy-2-methylpropionyl)piperazin-1-yl, 4-(2-hydroxyacetyl)piperazin-1-yl, 4-(2 hydroxyethylsulphonyl)piperazin-1-yl, 4-(2-hydroxypropionyl)piperazin-1-yl, 4-(2 mesylacetyl)piperazin-1-yl, 4-(2 methoxyacetyl)piperazin-1-yl, 4-(2-methoxyethylsulphonyl)piperazin-1 yl, 4-(2-methyl-2-hydroxypropionyl)piperazin-1-yl, 4-(2 methylpropionyl)piperazin 1-yl, 4-(2-morpholinoacetyl)piperazin 1 yl, 4-(2-pyrrolidin 1-ylacetyl)piperazin-1-yl, 4-(3-dimethyaminopropionyl)piperazin-1 yl, 4-(3-hydroxy-2,2-dimethylpropionyl)piperazin 1-yl, 4-(3-hydroxypropionyl)piperazin-1-yl, 4-(3-methoxypropionyl)piperazin 1-yl, 4-(3-methyl-3-hydroxybutanoyl)piperazin 1-yl, 4-(4-hydroxybutanoyl)piperazin-1-yl, 4-(acetoxyacetyl)piperazin-1 yl, 4-(acetyl)piperazin-1-yl, 4-(azetidin-1-ylacetyl)piperazin-1-yl, 4-(chloroacetyl)piperazin-1-yl, 4-(cyclopropyl)piperazin-1 yl, 4-(propionyl)piperazin-1-yl, 4-(tetrahydrofur-3 ylcarbonyl)piperazin-1-yl, 4-(vinylsulphonyl)piperazin-1-yl, 4-[2-(1*H* tetrazol-5-yl)acetyl)piperazin-1-yl, 4-[2-(2-propynyloxy)acetyl]piperazin 1-yl, 4-[2-(*N*-hydroxymethyl-*N*-methylamino)acetyl]piperazin 1-yl, 4-[2-(tetrazol-1-yl)acetyl]piperazin-1-yl, 4-acetylpiperazin-1 yl, 4-mesylpiperazin-1-yl, morpholino, and piperazin-1-yl

Ring A is 4-methylsulphonylpiperazin-1-yl, 4-vinylsulphonylpiperazin-1-yl, 4-acetylpiperazin-1-yl, 4-(acetoxyacetyl)piperazin-1-yl, 4-(hydroxyacetyl)piperazin-1-yl, 4-(dimethylaminoacetyl)piperazin-1-yl, 4-(2-dimethylaminoethylsulphonyl)piperazin-1-yl, 4-(2-methoxyethylsulphonyl)piperazin-1-yl, 4-(2-hydroxyethylsulphonyl)piperazin-1-yl, piperazin-1-yl or morpholino

R^1 is halo or C_{1-6}alkyl.

R^1 is fluoro, chloro or methyl.

p is 0-2, wherein the values of R^1 may be the same or different.

p is 0 or 1

p is 1

p is 0

R^2 is selected from hydroxy, amino, azido, C_{1-6}alkyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, carbocyclyl-R^{34}-, NHR^9 or -O-R^{12},

R^9 and R^{12} are independently selected from C_{1-6}alkanoyl or C_{1-6}alkylsulphonyl wherein R^9 and R^{12} may be independently optionally substituted on carbon by a group selected from R^{20},

R^{20} is hydroxy, and

R^{34} is -N(R^{29})C(O)-, wherein R^{29} is hydrogen.

R^2 is selected from hydroxy, amino, azido, methyl, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, cyclopropyl R^{34}-, -NHR^9 or -O-R^{12},

R^9 and R^{12} are independently selected from acetyl, propionyl or mesyl, wherein R^9 and R^{12} may be independently optionally substituted on carbon by a group selected from R^{20},

R^{20} is hydroxy; and

R^{34} is -N(R^{29})C(O)-, wherein R^{29} is hydrogen.

R^2 is selected from hydroxy, amino, azido, methyl, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, acetamido, {[(2*S*)-2-hydroxypropanoyl]amino}, glycoloylamino, mesylamino, 2-hydroxyacetamido, mesyloxy or *N*-cyclopropylcarbamoyl.

q is 0 or 1

q is 2

q is 1

q is 0

R^3 is halo.

R^3 is fluoro or chloro

R^3 is 5-fluoro or 5-chloro

R^3 is 5-fluoro

R^3 is 5-chloro

n is 0 or 1

n is 1

n is 0

R^4 is C_{1-6}alkyl or carbocyclyl, wherein R^4 may be optionally substituted on carbon by one or more R^{14}, wherein

R^{14} is carbocyclyl

R^4 is C_{1-4}alkyl or cyclobutyl, wherein R^4 may be optionally substituted on carbon by one or more R^{14}, wherein

R^{14} is cyclopropyl

R^4 is ethyl, isopropyl, isobutyl, cyclobutyl or cyclopropylmethyl

R^4 is isopropyl

R^5 and R^6 are independently selected from hydrogen or C_{1-6}alkyl, wherein R^5 and R^6 independently of each other may be optionally substituted on carbon by one or more R^{16}, wherein

R^{16} is selected from methoxy

R^5 and R^6 are independently selected from hydrogen methyl, ethyl or propyl, wherein R^5 and R^6 independently of each other may be optionally substituted on carbon by one or more R^{16}, wherein

R^{16} is selected from methoxy

R^5 and R^6 are independently selected from hydrogen, methyl, ethyl, methoxymethyl, propyl

R^5 is C_{1-6}alkyl, wherein R^5 may be optionally substituted on carbon by one or more R^{16}, wherein

R^{16} is methoxy

R^5 is C_{1-4}alkyl, wherein R^5 may be optionally substituted on carbon by one or more R^{16}, wherein

R^{16} is methoxy

R^5 is methyl, ethyl, propyl or methoxymethyl

R^5 is methyl.

R^6 is hydrogen.

R^4 is isopropyl, R^5 is methyl and R^6 is hydrogen.

Therefore in a further aspect of the invention there is provided a compound of formula (I) (as depicted above) wherein.

Ring A is a nitrogen linked 4-7 membered saturated ring which optionally contains an additional nitrogen or oxygen atom, wherein if Ring A contains an additional nitrogen atom that nitrogen may be optionally substituted by R^7,

R^1 is halo or C_{1-6}alkyl,

p is 0 or 1,

R^2 is selected from hydroxy, amino, azido, C_{1-6}alkyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, carbocyclyl-R^{34}-, NHR^9 or -O-R^{12},

q is 0-2, wherein the values of R^2 maybe the same or different;

R^3 is halo

n is 0 or 1,

R^4 is C_{1-6}alkyl or carbocyclyl, wherein R^4 may be optionally substituted on carbon by one or more R^{14},

R^5 and R^6 are independently selected from hydrogen or C_{1-6}alkyl, wherein R^5 and R^6 independently of each other may be optionally substituted on carbon by one or more R^{16},

R^7 is selected from C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{2-6}alkenylsulphonyl, carbocyclyl R^{18}- or heterocyclyl-R^{19}-, wherein R^7 may be independently optionally substituted on carbon by a group selected from R^{20}, and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by R^{21},

R^9 and R^{12} are independently selected from C_{1-6}alkanoyl or C_{1-6}alkylsulphonyl, wherein R^9 and R^{12} may be independently optionally substituted on carbon by a group selected from R^{20},

R^{14} is carbocyclyl,

R^{16} is selected from methoxy;

R^{18} and R^{19} are -C(O)-,

R^{20} is selected from halo, cyano, hydroxy, C_{1-6}alkoxy, C_{2-6}alkynyloxy, C_{1-6}alkanoyloxy, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkylS(O)$_a$ wherein a is 2 or heterocyclyl, wherein R^{20} may be optionally substituted on carbon by one or more R^{26},

R^{21} is C_{1-6}alkyl,

R^{26} is hydroxy, or

R^{34} is -N(R^{29})C(O)-, wherein R^{29} is hydrogen,

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Therefore in a further aspect of the invention there is provided a compound of formula (I) (as depicted above) wherein

Ring A, R^2 and q together form piperazin-1-yl, morpholino, 4-mesylpiperazin-1 yl, 4-acetylpiperazin-1-yl, 4-(2-acetoxyacetyl)piperazin-1-yl, 4-(2-hydroxyacetyl)piperazin-1-yl, 4-(2-chloroacetyl)piperazin-1-yl, 4-(2-methoxyacetyl)piperazin-1-yl, (3 methoxypropanoyl)piperazin-1-yl (3-hydroxy-3 methylbutanoyl)piperazin-1 yl, (3-hydroxy-2,2-dimethylpropanoyl)piperazin 1-yl, ((R)-3-methyl 2 hydroxybutanoyl)piperazin 1-yl, ((S)-3-methyl 2-hydroxybutanoyl)piperazin-1 yl, 4-(2-dimethylaminoacetyl)piperazin-1-yl, 4-[2-(dimethylamino)ethylsulphonyl]piperazin 1 yl, 4-[2-(methoxy)ethylsulphonyl]piperazin-1-yl, 4-[2-(hydroxy)ethylsulphonyl]piperazin 1-yl, 4-(cyclopropylcarbonyl)piperazin-1-yl, 4-(1-hydroxycyclopropylcarbonyl)piperazin-1-yl, 4-(1-cyanocyclopropylcarbonyl)piperazin 1-yl, 4-(2-hydroxy 2-methylpropanoyl)piperazin-1-yl, 4-((R)-2-hydroxypropanoyl)piperazin-1-yl, 4-((S)-2-hydroxypropanoyl)piperazin-1 yl, 4-((R)-2-methoxypropanoyl)piperazin-1 yl, 4-((S)-2-methoxypropanoyl)piperazin-1 yl, 4-((R) tetrahydrofuran-2-ylcarbonyl)piperazin 1-yl 4-((S)-tetrahydrofuran-2-ylcarbonyl)piperazin-1-yl, 4-(isobutyryl)piperazin-1-yl, 4-((R)-2-hydroxybutanoyl)piperazin-1-yl, 4-((S)-2- hydroxybutanoyl)piperazin-1 yl, (R)-3-acetylaminopyrrolidin-1-yl, (S)-3-acetylaminopyrrolidin-1-yl, (R)-2-(cyclopropylaminocarbonyl)pyrrolidin 1 yl, (R)-2 (*N*-methylcarbamoyl)pyrrolidin-1-yl, (S)-2-(*N*,*N*-dimethylcarbamoyl)pyrrolidin 1-yl, 4-(ethenylsulphonyl)piperazin-1-yl, 4-[2-(2-propyn-1 yloxy)acetyl]piperazin-1 yl, 4-(tetrahydrofuran-3 ylcarbonyl)piperazin-1 yl, 4-(3-dimethylaminopropanoyl)piperazin-1-yl, 4-[2-(*N*-methyl-*N*-hydroxymethylamino)acetyl]piperazin 1-yl, 4-[3-hydroxy 2-(hydroxymethyl)propanoyl]piperazin 1 yl, 4-[2-(1,2,3,4-tetrazol 1-yl)acetyl]piperazin-1-yl, 4-[2-(1,2,3,4-tetrazol-5-yl)acetyl]piperazin-1-yl, 4-(1-methyl-L-prolyl)piperazin-1-yl, 4-[2-(mesyl)acetyl]piperazin-1-yl, 4-(2,2-difluoroacetyl)piperazin-1-yl, 4-[2-(pyrrolidin-1-yl)acetyl]piperazin 1-yl, 4-[2-(morpholino)acetyl]piperazin-1-yl, 4-[2-(diethylamino)acetyl]piperazin-1 yl, 4-(propionyl)piperazin-1-yl, 4-(3-hydroxypropionyl)piperazin-1-yl, 4-[2-(azetidin 1-yl)acetyl]piperazin 1 yl, (R) 3-aminopyrrolidin-1-yl, (S)-3-aminopyrrolidin 1-yl, (3*R*,5*S*)-4-acetyl 3,5-dimethylpiperazin-1-yl, (2*S*,5*R*)-4-acetyl 2,5-dimethylpiperazin-1 yl, (2*RS*,6*SR*)-2,6-dimethylmorpholin-4-yl]phenyl, 3-hydroxyazetidin-1-yl, 3-acetylaminoazetidin 1-yl, 3-(2-hydroxyacetylamino)azetidin-1-yl, 3-mesylaminoazetidin-1-yl, 3-mesyloxyazetidin-1-yl, 3

azidoazetidin-1-yl, 3-aminoazetidin-1-yl, (3*R*) 3-{[(2*S*)-2-hydroxypropanoyl]amino}pyrrolidin-1-yl, (3*S*) 3 {[(2*S*)-2-hydroxypropanoyl]amino}pyrrolidin-1 yl (3*S*)-3-(glycoloylamino)pyrrolidin-1-yl and (3*R*)-3-(glycoloylamino)pyrrolidin-1 yl,

R^1 is fluoro, chloro or methyl,

p is 0 or 1,

R^2 is selected from hydroxy, amino, azido, methyl, *N* methylcarbamoyl, *N,N*-dimethylcarbamoyl, acetamido, {[(2*S*)-2-hydroxypropanoyl]amino}, glycoloylamino, mesylamino 2-hydroxyacetamido mesyloxy or *N*-cyclopropylcarbamoyl.

q is 0-2, wherein the values of R^2 maybe the same or different,

R^3 is 5-fluoro or 5-chloro,

n is 0 or 1,

R^4 is ethyl, isopropyl, isobutyl, cyclobutyl or cyclopropylmethyl,

R^5 and R^6 are independently selected from hydrogen, methyl, ethyl, methoxymethyl, propyl,

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof

Therefore in a further aspect of the invention there is provided a compound of formula (I) (as depicted above) wherein.

Ring A is a nitrogen linked 4-7 membered saturated ring which optionally contains an additional nitrogen, oxygen or sulphur atom, wherein if Ring A contains an additional nitrogen atom that nitrogen may be optionally substituted by R^7, wherein

R^3 is halo,

R^4 is C_{1-6}alkyl or carbocyclyl, wherein R^4 may be optionally substituted on carbon by one or more R^{14}, wherein

R^5 and R^6 are independently selected from hydrogen or C_{1-6}alkyl, wherein R^5 and R^6 independently of each other may be optionally substituted on carbon by one or more R^{16},

R^7 is selected from C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{2-6}alkenylsulphonyl, carbocyclyl R^{18} or heterocyclyl-R^{19}-, wherein R^7 may be independently optionally substituted on carbon by a group selected from R^{20}, and wherein if said heterocyclyl contains an NH- moiety that nitrogen may be optionally substituted by R^{21},

R^{14} is carbocyclyl,

R^{16} is selected from methoxy,

R^{18} and R^{19} are -C(O)-,

R^{20} is selected from halo, cyano, hydroxy, C_{1-6}alkoxy, C_{2-6}alkynyloxy, C_{1-6}alkanoyloxy, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkylS(O)$_n$ wherein a is 2 or heterocyclyl, wherein R^{20} may be optionally substituted on carbon by one or more R^{26},

R^{21} is C_{1-6}alkyl,

R^{26} is hydroxy,

p is 0,

q is 0,

n is 0 or 1,

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Therefore in a further aspect of the invention there is provided a compound of formula (I) (as depicted above) wherein

Ring A is a nitrogen linked 6 membered saturated ring which optionally contains an additional nitrogen atom, wherein if Ring A contains an additional nitrogen atom that nitrogen may be optionally substituted by R^7 wherein

R^7 is selected from C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl and C_{2-6}alkenylsulphonyl, wherein R^7 may be optionally substituted on carbon by a group selected from R^{20}, wherein

R^{20} is selected from hydroxy C_{1-6}alkoxy, C_{1-6}alkanoyloxy and *N,N*-(C_{1-6}alkyl)$_2$amino

p is 0,

q is 0,

R^3 is halo,

n is 0 or 1

R^4 is C_{1-6}alkyl or carbocyclyl, wherein R^4 may be optionally substituted on carbon by one or more R^{14}, wherein

R^{14} is carbocyclyl,

R^5 is C_{1-6}alkyl, wherein R^5 may be optionally substituted on carbon by one or more R^{16} wherein

R^{16} is methoxy, and

R^6 is hydrogen.

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Therefore in a further aspect of the invention there is provided a compound of formula (I) (as depicted above) wherein

Ring A is 4-methylsulphonylpiperazin-1-yl, 4-vinylsulphonylpiperazin-1 yl, 4-acetylpiperazin-1 yl, 4-(acteoxyacetyl)piperazin-1-yl, 4-(hydroxyacetyl)piperazin-1 yl, 4-

(dimethylaminoacetyl)piperazin-1-yl, 4-(2-dimethylaminoethylsulphonyl)piperazin-1-yl, 4-(2-methoxyethylsulphonyl)piperazin-1 yl, 4-(2-hydroxyethylsulphonyl)piperazin-1 yl, piperazin-1 yl or morpholino,

p is 0,

q is 0,

R^3 is halo,

n is 0 or 1,

R^4 is ethyl, isopropyl, isobutyl, cyclobutyl or cyclopropylmethyl,

R^5 is methyl, ethyl propyl or methoxymethyl, and

R^6 is hydrogen,

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

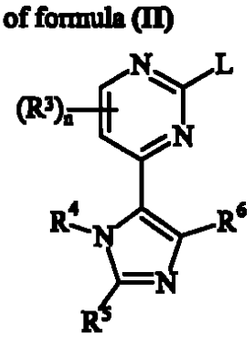
In another aspect of the invention, preferred compounds of the invention are any one of the Examples or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

In another aspect of the invention, preferred compounds of the invention are any one of Examples 18 22, 87, 92, 94, 96, 104 113, 118 or 121, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof

Preferred aspects of the invention are those which relate to the compound of formula (I) or a pharmaceutically acceptable salt thereof.

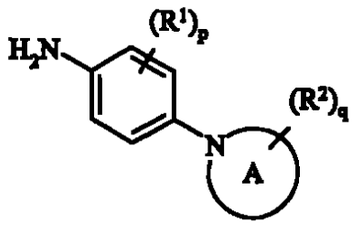
Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula (I)) comprises of

Process a) reaction of a pyrimidine of formula (II)



(II)

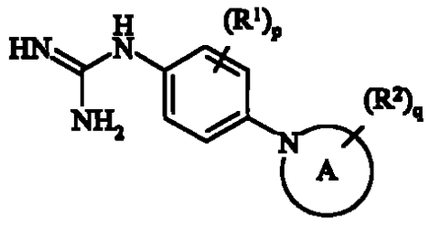
wherein L is a displaceable group, with an aniline of formula (III)



(III)

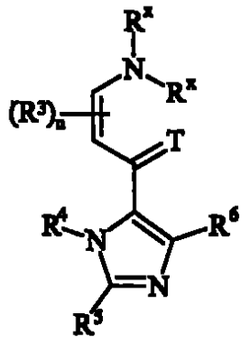
or

Process b) reacting a compound of formula (IV)



(IV)

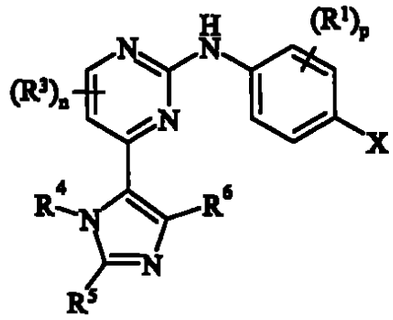
with a compound of formula (V)



(V)

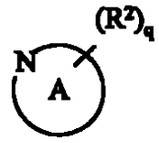
wherein T is O or S R^x may be the same or different and is selected from C_{1-6}alkyl, or

Process c) reacting a pyrimidine of formula (VI)



(VI)

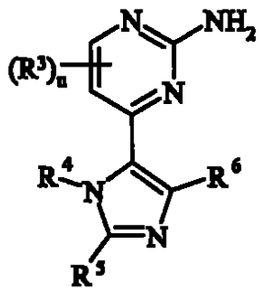
wherein X is a displaceable group, with a heterocyclyl of formula (VII)



(VII)

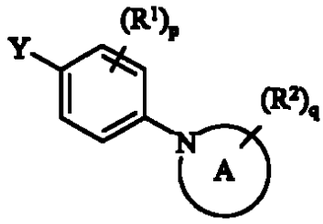
or

Process d) for compounds of formula (I), reacting a pyrimidine of formula (VIII)



(VIII)

with a compound of formula (IX)



(IX)

where Y is a displaceable group,

and thereafter if necessary

i) converting a compound of the formula (I) into another compound of the formula (I)

ii) removing any protecting groups,

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester

L is a displaceable group, suitable values for L are for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group

X is a displaceable group, suitable values for X are for example, a bromo or iodo group. Preferably X is bromo.

Y is a displaceable group, suitable values for Y are for example, a halogeno or sulphonyloxy group, for example a bromo, iodo or trifluoromethanesulphonyloxy group.

Preferably Y is iodo

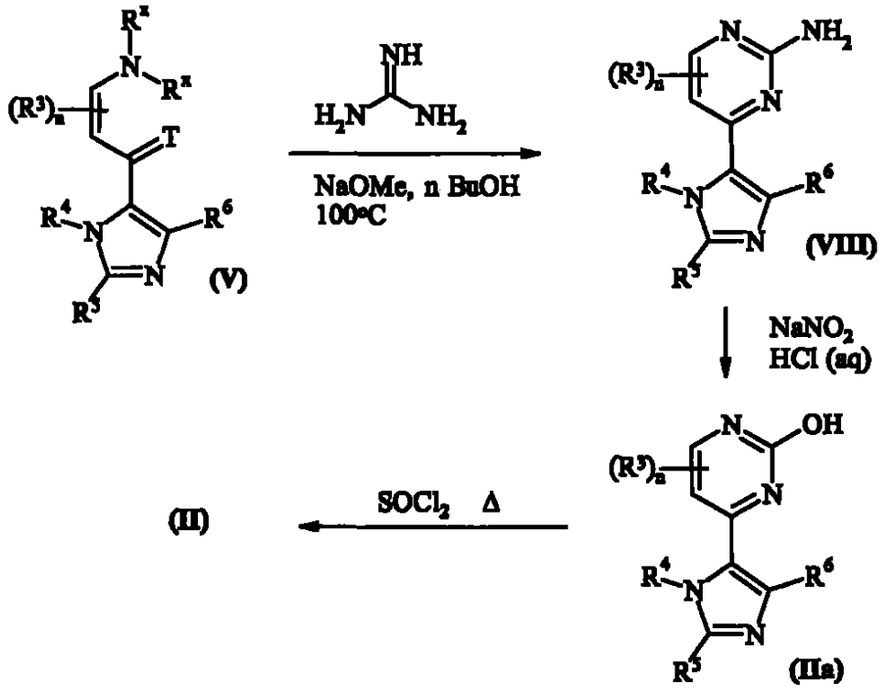
Specific reaction conditions for the above reactions are as follows

Process a) Pyrimidines of formula (II) and anilines of formula (III) may be reacted together

i) in the presence of a suitable solvent for example a ketone such as acetone or an alcohol such as ethanol or butanol or an aromatic hydrocarbon such as toluene or *N*-methyl pyrrolidine, optionally in the presence of a suitable acid for example an inorganic acid such as hydrochloric acid or sulphuric acid, or an organic acid such as acetic acid or formic acid (or a suitable Lewis acid) and at a temperature in the range of 0°C to reflux, preferably reflux, or

ii) under standard Buchwald conditions (for example see *J Am. Chem Soc.*, 118, 7215, *J Am. Chem Soc.*, 119, 8451, *J Org Chem.*, 62, 1568 and 6066) for example in the presence of palladium acetate, in a suitable solvent for example an aromatic solvent such as toluene, benzene or xylene, with a suitable base for example an inorganic base such as caesium carbonate or an organic base such as potassium-*t* butoxide, in the presence of a suitable ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and at a temperature in the range of 25 to 80°C

Pyrimidines of the formula (II) where L is chloro may be prepared according to *Scheme 1*

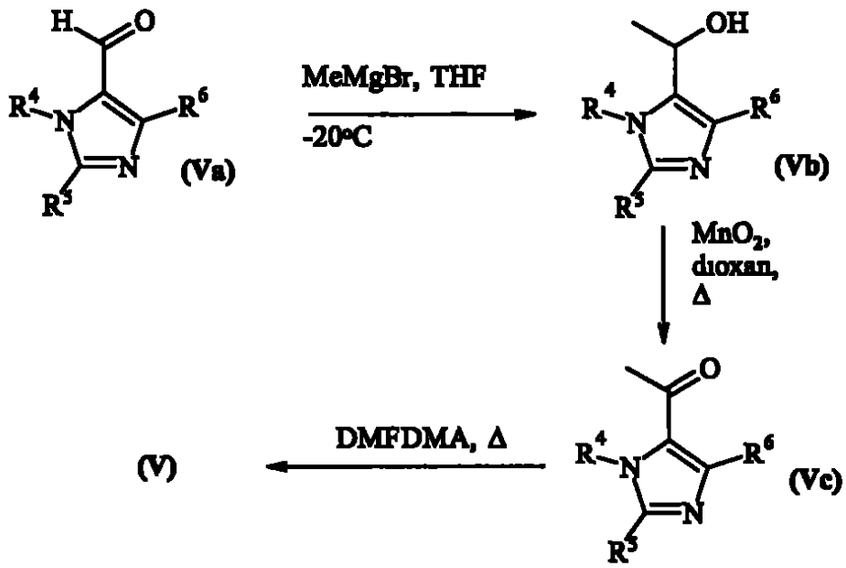


Scheme 1

Anilines of formula (III) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process b) Compounds of formula (IV) and compounds of formula (V) are reacted together in a suitable solvent such as *N*-methylpyrrolidinone or butanol at a temperature in the range of 100-200°C, preferably in the range of 150-170°C. The reaction is preferably conducted in the presence of a suitable base such as, for example, sodium hydride, sodium methoxide or potassium carbonate.

Compounds of formula (V) may be prepared according to *Scheme 2*



Scheme 2

Compounds of formula (IV) and (Va) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process c) Compounds of formula (VI) and amines of formula (VII) may be reacted together under standard Buchwald conditions (for example see *J Am Chem Soc*, **118**, 7215, *J Am. Chem. Soc* **119**, 8451, *J Org Chem*, **62**, 1568 and 6066) for example in the presence of palladium acetate, in a suitable solvent for example an aromatic solvent such as toluene, benzene or xylene, with a suitable base for example an inorganic base such as caesium carbonate or an organic base such as potassium *t*-butoxide, in the presence of a suitable ligand such as 2,2'-bis(diphenylphosphino)-1,1' binaphthyl and at a temperature in the range of 25 to 80°C

Compounds of formula (VI) may be prepared according to the procedures described in WO 02/20512

Heterocyclyls of formula (VII) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process d) Compounds of formula (VIII) and amines of formula (IX) may be reacted together under standard Buchwald conditions as described in *Process a*

The synthesis of compounds of formula (VIII) is described in *Scheme 1*

Compounds of formula (IX) are commercially available compounds or they are known in the literature, or they are prepared by standard processes known in the art.

Amines of formula (VI) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions, the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions, and the introduction of a halogeno group Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating, oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

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

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t* butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

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

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

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

As stated hereinbefore the compounds defined in the present invention possesses anti-cell-proliferation activity such as anti-cancer activity which is believed to arise from the

CDK inhibitory activity of the compound. These properties may be assessed, for example, using the procedure set out below

Assay

The following abbreviations have been used -

HEPES is *N* [2-Hydroxyethyl]piperazine-*N'*-[2-ethanesulfonic acid]

DTT is Dithiothreitol

PMSF is Phenylmethylsulphonyl fluoride

The compounds were tested in an *in vitro* kinase assay in 96 well format using Scintillation Proximity Assay (SPA - obtained from Amersham) for measuring incorporation of [γ-33-P]-Adenosine Triphosphate into a test substrate (GST-Retinoblastoma protein, GST-Rb). In each well was placed the compound to be tested (diluted in DMSO and water to correct concentrations) and in control wells either roscovitine as an inhibitor control or DMSO as a positive control.

Approximately 0.2µl of CDK2/Cyclin E partially-purified enzyme (amount dependent on enzyme activity) diluted in 25µl incubation buffer was added to each well then 20µl of GST-Rb/ATP/ATP33 mixture (containing 0.5µg GST-Rb and 0.2µM ATP and 0.14µCi [γ-33-P]-Adenosine Triphosphate in incubation buffer), and the resulting mixture shaken gently, then incubated at room temperature for 60 minutes.

To each well was then added 150µL stop solution containing (0.8mg/well of Protein A-PVT SPA bead (Amersham)), 20pM/well of Anti-Glutathione Transferase, Rabbit IgG (obtained from Molecular Probes), 61mM EDTA and 50mM HEPES pH 7.5 containing 0.05% sodium azide.

The plates were sealed with Topseal S plate sealers, left for two hours then spun at 2500rpm, 1124xg , for 5 minutes. The plates were read on a Topcount for 30 seconds per well.

The incubation buffer used to dilute the enzyme and substrate mixes contained 50mM HEPES pH7.5, 10mM $MnCl_2$, 1mM DTT, 100µM Sodium vanadate, 100µM NaF, 10mM Sodium Glycerophosphate, BSA (1mg/ml final)

Test substrate

In this assay only part of the retinoblastoma protein (Science 1987 Mar13, 235 (4794) 1394-1399, Lee W H., Bookstein R., Hong F., Young L.J., Shew J Y., Lee E Y.) was used, fused to a GST tag. PCR of retinoblastoma gene encoding amino acids 379-928 (obtained from retinoblastoma plasmid ATCC pLRbRNL) was performed, and the sequence

cloned into pGEx 2T fusion vector (Smith D B and Johnson, K S Gene 67, 31 (1988), which contained a tac promoter for inducible expression, internal lac I^q gene for use in any E Coli host, and a coding region for thrombin cleavage - obtained from Pharmacia Biotech) which was used to amplify amino acids 792-928 This sequence was again cloned into pGEx 2T

The retinoblastoma 792-928 sequence so obtained was expressed in E.Coli (BL21 (DE3) pLysS cells) using standard inducible expression techniques, and purified as follows

E coli paste was resuspended in 10ml/g of NETN buffer (50mM Tris pH 7 5, 120mM NaCl, 1mM EDTA, 0 5%v/v NP-40, 1mM PMSF, 1ug/ml leupeptin, 1ug/ml aprotinin and 1ug/ml pepstatin) and sonicated for 2 x 45 seconds per 100ml homogenate After centrifugation, the supernatant was loaded onto a 10ml glutathione Sepharose column (Pharmacia Biotech, Herts, UK), and washed with NETN buffer After washing with kinase buffer (50mM HEPES pH 7 5, 10mM $MgCl_2$, 1mM DTT 1mM PMSF, 1ug/ml leupeptin, 1ug/ml aprotinin and 1ug/ml pepstatin) the protein was eluted with 50mM reduced glutathione in kinase buffer Fractions containing GST Rb(792-927) were pooled and dialysed overnight against kinase buffer The final product was analysed by Sodium Dodeca Sulfate (SDS) PAGE (Polyacrylamide gel) using 8-16% Tris-Glycine gels (Novex, San Diego USA)

<u>CDK2 and Cyclin E</u>

The open reading frames of CDK2 and Cyclin E were isolated by reverse transcriptase-PCR using HeLa cell and activated T cell mRNA as a template and cloned into the insect expression vector pVL1393 (obtained from Invitrogen 1995 catalogue number V1392-20) CDK2 and cyclin E were then dually expressed [using a standard virus Baculogold co-infection technique] in the insect SF21 cell system (Spodoptera Frugiperda cells derived from ovarian tissue of the Fall Army Worm commercially available)

<u>Example production of Cyclin E/CDK2</u>

The following Example provides details of the production of Cyclin E/CDK2 in SF21 cells (in TC100 + 10% FBS(TCS) + 0 2% Pluronic) having dual infection MOI 3 for each virus of Cyclin E & CDK2

SF21 cells grown in a roller bottle culture to 2 33 x 10^6 cells/ml were used to inoculate 10 x 500 ml roller bottles at 0 2 x 10E6 cells/ml. The roller bottles were incubated on a roller rig at 28°C

After 3 days (72 hrs) the cells were counted, and the average from 2 bottles found to be 1 86 x 10E6 cells/ml (99% viable) The cultures were then infected with the dual viruses at an MOI 3 for each virus

The viruses were mixed together before addition to the cultures, and the cultures returned to the roller rig 28°C

After 2 days (48 hrs) post infection the 5 Litres of culture was harvested. The total cell count at harvest was 1 58 x 10E6 cells/ml.(99% viable) The cells were spun out at 2500rpm, 30 mins., 4°C in Heraeus Omnifuge 2 0 RS in 250 ml lots The supernatant was discarded.

Partial co-purification of Cdk2 and Cyclin E

Sf21 cells were resuspended in lysis buffer (50mM Tris pH 8.2, 10mM $MgCl_2$, 1mM DTT, 10mM glycerophosphate, 0 1mM sodium orthovanadate, 0 1mM NaF, 1mM PMSF, 1ug/ml leupeptin and 1ug/ml aprotinin) and homogenised for 2 minutes in a 10ml Dounce homgeniser After centrifugation, the supernatant was loaded onto a Poros HQ/M 1 4/100 anion exchange column (PE Biosystems, Hertford, UK) Cdk2 and Cyclin E were coeluted at the beginning of a 0-1M NaCl gradient (run in lysis buffer minus protease inhibitors) over 20 column volumes Co-elution was checked by western blot using both anti-Cdk2 and anti Cyclin E antibodies (Santa Cruz Biotechnology, California, US)

By analogy, assays designed to assess inhibition of CDK1 and CDK4 may be constructed CDK2 (EMBL Accession No X62071) may be used together with Cyclin A or Cyclin E (see EMBL Accession No M73812), and further details for such assays are contained in PCT International Publication No WO99/21845, the relevant Biochemical & Biological Evaluation sections of which are hereby incorporated by reference

Although the pharmacological properties of the compounds of the formula (I) vary with structural change, in general activity possessed by compounds of the formula (I) may be demonstrated at IC_{50} concentrations or doses in the range 250μM to 1nM

When tested in the above in-vitro assay the CDK2 inhibitory activity of Example 8 was measured as IC_{50} = 0 181μM

The *in vivo* activity of the compounds of the present invention may be assessed by standard techniques, for example by measuring inhibition of cell growth and assessing cytotoxicity

Inhibition of cell growth may be measured by staining cells with Sulforhodamine B (SRB), a fluorescent dye that stains proteins and therefore gives an estimation of amount of

protein (i.e. cells) in a well (see Boyd, M.R.(1989) Status of the NCI preclinical antitumour drug discovery screen. Prin. Prac Oncol 10 1 12). Thus, the following details are provided of measuring inhibition of cell growth -

Cells were plated in appropriate medium in a volume of 100ml in 96 well plates, media was Dulbecco's Modified Eagle media for MCF-7, SK-UT-1B and SK UT-1. The cells were allowed to attach overnight, then inhibitor compounds were added at various concentrations in a maximum concentration of 1% DMSO (v/v). A control plate was assayed to give a value for cells before dosing. Cells were incubated at 37°C, (5% CO_2) for three days.

At the end of three days TCA was added to the plates to a final concentration of 16% (v/v). Plates were then incubated at 4°C for 1 hour, the supernatant removed and the plates washed in tap water. After drying, 100ml SRB dye (0.4% SRB in 1% acetic acid) was added for 30 minutes at 37°C. Excess SRB was removed and the plates washed in 1% acetic acid. The SRB bound to protein was solubilised in 10mM Tris pH7.5 and shaken for 30 minutes at room temperature. The ODs were read at 540nm, and the concentration of inhibitor causing 50% inhibition of growth was determined from a semi-log plot of inhibitor concentration versus absorbance. The concentration of compound that reduced the optical density to below that obtained when the cells were plated at the start of the experiment gave the value for toxicity.

Typical IC_{50} values for compounds of the invention when tested in the SRB assay are in the range 1mM to 1nM.

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

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

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

The compound of formula (I) will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose.

A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, are effective cell cycle inhibitors (anti-cell proliferation agents), which property is believed to arise from their CDK inhibitory properties. Accordingly the compounds of the present invention are expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by CDK enzymes, i.e. the compounds may be used to produce a CDK inhibitory effect in a warm blooded animal in need of such treatment. Thus the compounds of the present invention provide a method for treating the proliferation of malignant cells characterised by inhibition of CDK enzymes, i.e. the compounds may be used to produce an anti proliferative effect mediated alone or in part by the inhibition of CDKs. Such a compound of the invention is expected to possess a wide range of anti-cancer properties as CDKs have been implicated in many common human cancers such as leukaemia and breast, lung, colon, rectal, stomach, prostate, bladder, pancreas and ovarian cancer. Thus it is expected that a compound of the invention will possess anti-cancer activity against these cancers. It is in addition expected that a compound of the present invention will possess activity against a range of leukaemias, lymphoid malignancies and solid tumours such as carcinomas and sarcomas in tissues such as the liver, kidney, prostate and pancreas. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. More particularly such compounds of the invention, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with CDKs, especially those tumours which are significantly dependent on CDKs for their growth and spread, including for example, certain tumours of the colon, breast, prostate, lung, vulva and skin.

Herein when cancer is referred to, in particular this refers to leukaemia, breast cancer, lung cancer, colon cancer, rectal cancer stomach cancer, prostate cancer, bladder cancer, cancer of the pancreas ovarian cancer, liver cancer, kidney cancer, skin cancer and cancer of the vulva.

It is further expected that a compound of the present invention will possess activity against other cell proliferation diseases in a wide range of other disease states including leukaemias, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

Thus according to this aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore for use as a medicament, and the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal such as man. Particularly, an inhibitory effect is produced by preventing entry into, or progression through, the S phase by inhibition of CDK2 and CDK4, especially CDK2, and M phase by inhibition of CDK1.

According to a further feature of the invention, there is provided a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before in the manufacture of a medicament for use in the treatment of cancers (solid tumours and leukaemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation, particularly in the treatment of cancers.

According to a further feature of the invention, there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before in the manufacture of a medicament for use in the treatment of cancer.

According to a further feature of the invention, there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable

ester thereof, as defined herein before in the manufacture of a medicament for use in the production of a CDK inhibitory effect.

According to a further feature of this aspect of the invention there is provided a method for producing a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound as defined immediately above. Particularly, an inhibitory effect is produced by preventing entry into, or progression through, the S phase by inhibition of CDK2 and CDK4, especially CDK2, and M phase by inhibition of CDK1

According to a further feature of this aspect of the invention there is provided a method for producing a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof as defined herein before. Particularly, an inhibitory effect is produced by preventing entry into or progression through, the S phase by inhibition of CDK2 and CDK4, especially CDK2, and M phase by inhibition of CDK1

According to an additional feature of this aspect of the invention there is provided a method of treating cancers (solid tumours and leukaemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation, in a warm blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof as defined herein before.

Particularly there is provided a method of treating cancer in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof as defined herein before

Particularly there is provided a method of producing a CDK inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof as defined herein before.

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In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the production of a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of cancers (solid tumours and leukaemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation, in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of cancer in a warm-blooded animal such as man.

In a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined herein before in association with a pharmaceutically acceptable diluent or carrier for use in the production of a CDK inhibitory effect in a warm-blooded animal such as man.

Preventing cells from entering DNA synthesis by inhibition of essential S-phase initiating activities such as CDK2 initiation may also be useful in protecting normal cells of the body from toxicity of cycle-specific pharmaceutical agents. Inhibition of CDK2 or 4 will prevent progression into the cell cycle in normal cells which could limit the toxicity of cycle-specific pharmaceutical agents which act in S phase, G2 or mitosis. Such protection may result in the prevention of hair loss normally associated with these agents.

Therefore in a further aspect of the invention there is provided a compound of formula (I) as defined above or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof for use as a cell protective agent.

Therefore in a further aspect of the invention there is provided a compound of formula (I) as defined above or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof for use in preventing hair loss arising from the treatment of malignant conditions with pharmaceutical agents

Examples of pharmaceutical agents for treating malignant conditions that are known to cause hair loss include alkylating agents such as ifosfamide and cyclophosphamide, antimetabolites such as methotrexate, 5 fluorouracil, gemcitabine and cytarabine; vinca alkaloids and analogues such as vincristine, vinbalstine, vindesine, vinorelbine, taxanes such as paclitaxel and docetaxel topoisomerase I inhibitors such as irintotecan and topotecan, cytotoxic antibiotics such as doxorubicin, daunorubicin, mitoxantrone, actinomycin D and mitomycin, and others such as etoposide and tretinoin.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof may be administered in association with a one or more of the above pharmaceutical agents In this instance the compound of formula (I) may be administered by systemic or non systemic means Particularly the compound of formula (I) my may administered by non-systemic means, for example topical administration.

Therefore in an additional feature of the invention, there is provided a method of preventing hair loss during treatment for one or more malignant conditions with pharmaceutical agents, in a warm-blooded animal, such as man, which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof

In an additional feature of the invention, there is provided a method of preventing hair loss during treatment for one or more malignant conditions with pharmaceutical agents, in a warm-blooded animal, such as man which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof in simultaneous, sequential or separate administration with an effective amount of said pharmaceutical agent.

According to a further aspect of the invention there is provided a pharmaceutical composition for use in preventing hair loss arising from the treatment of malignant conditions with pharmaceutical agents which comprises a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, and said pharmaceutical agent, in association with a pharmaceutically acceptable diluent or carrier

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According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, and a pharmaceutical agent for treating malignant conditions that is known to cause hair loss.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, in a first unit dosage form,

b) a pharmaceutical agent for treating malignant conditions that is known to cause hair loss, in a second unit dosage form, and

c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, in the manufacture of a medicament for the prevention of hair loss during treatment of malignant conditions with pharmaceutical agents.

According to a further aspect of the present invention there is provided a combination treatment for the prevention of hair loss comprising the administration of an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of a pharmaceutical agent for treatment of malignant conditions to a warm-blooded animal, such as man.

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

The CDK inhibitory activity defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the cell cycle inhibitory treatment defined hereinbefore may be

surgery, radiotherapy or chemotherapy Such chemotherapy may cover three main categories of therapeutic agent.

(i) other cell cycle inhibitory agents that work by the same or different mechanisms from those defined hereinbefore,

(ii) cytostatic agents such as antioestrogens (for example tamoxifen,toremifene, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrazole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide) inhibitors of testosterone 5α-dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors), and

(iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside), antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin), platinum derivatives (for example cisplatin, carboplatin), alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa), antimitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere), topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan) According to this aspect of the invention there is provided a pharmaceutical product comprising a compound of the formula (I) as defined hereinbefore and an additional anti tumour substance as defined herembefore for the conjoint treatment of cancer

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

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply

Examples

The invention will now be illustrated by the following non limiting examples in which, unless stated otherwise

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

(ii) organic solutions were dried over anhydrous magnesium sulphate, evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals, 4 5-30mmHg) with a bath temperature of up to 60°C,

(iii) chromatography means flash chromatography on silica gel, thin layer chromatography (TLC) was carried out on silica gel plates,

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectral data,

(vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development, preparations were repeated if more material was required,

(vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeutero dimethyl sulphoxide (DMSO-d_6) as solvent unless otherwise indicated, ^{19}F NMR is also recorded in DMSO-d_6 unless otherwise stated,

(viii) chemical symbols have their usual meanings, SI units and symbols are used,

(ix) solvent ratios are given in volume volume (v/v) terms, and

(x) mass spectra were run with an electron energy of 70 electron volts in the chemical ionization (CI) mode using a direct exposure probe, where indicated ionization was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP), values for m/z are given, generally, only ions which indicate the parent mass are reported, and unless otherwise stated, the mass ion quoted is $(MH)^+$

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

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

(xvi) the following abbreviations have been used

THF	tetrahydrofuran,
DMF	*N,N*-dimethylformamide,
DMFDMA	dimethylformamide dimethylacetal,
EtOAc	ethyl acetate,
MeOH	methanol,
EtOH	ethanol,
DIPEA	*N,N*-diisopropylethylamine,
HATU	*O*-(7-azabenzotriazol-1-yl)-1,1-3 3-tetramethyluronium hexafluorophosphate,
HOBt	1-hydroxybenzotriazole
EDAC	1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide hydrochloride
ether	diethyl ether;
TFA	trifluoroacetic acid,
DCM	dichloromethane, and
DMSO	dimethylsulphoxide.

xvii) where an Isolute SCX 2 column is referred to, this means an "ion exchange" extraction cartridge for adsorption of basic compounds, i.e. a polypropylene tube containing a benzenesulphonic acid based strong cation exchange sorbent, used according to the manufacturers instructions obtained from International Sorbent Technologies Limited, Dyffryn Business Park, Hengeod, Mid Glamorgan, UK, CF82 7RJ,

xviii) where an Isolute amine column is referred to, this means an "ion exchange" extraction cartridge for adsorption of acidic compounds, i.e. a polypropylene tube containing a amino silane covalently bonded to a silica particle used according to the manufacturers instructions obtained from International Sorbent Technologies Limited, Dyffryn Business Park, Hengeod, Mid Glamorgan, UK, CF82 7RJ,

xix) where a Chemelut column is referred to, this means an extraction cartridge for removal of water, i.e. a polypropylene tube containing diatomaceous earth used according to the manufacturers instructions obtained from Varian, Harbor City California, USA, and

xx) where HPLC was performed on a Phenomenex column this refers to a Phenomenex 150 x 21 2 mm Luna 10 micron C18 column using a gradient of 5 to 95 of 0 2% TFA water - acetonitrile over 10mins at 20 ml / minute flow rate,

xxi) macroporous polystyrene carbonate resin refers to, Argonaut Technologies MP carbonate resin with the capacity 3 0 Mole equivalents per gram of resin available from Argonaut Technologies , New Road, Hengoed, Mid Glamorgan United Kingdom, CF82 8AU

Example 1

2-[4-(4-Mesylpiperazin-1-yl)anilino]-4-(1 isopropyl-2-methyl-1*H*-imidazol-5 yl)pyrimidine

2-Amino-4-(1 isopropyl-2-methyl 1*H* imidazol-5 yl)pyrimidine (Method 39 of WO 03/076436, 220mg, 1mmol) 1-bromo-4-(4-mesylpiperazinyl)benzene (WO 2001062742, 319mg, 1mmol), tris(dibenzylideneacetone)dipalladium(0) (23mg, 2mol%), 2-(di-tert-butylphosphino)biphenyl (6mg, 2 mol%) and sodium tert-butoxide (135 mg, 1 4 mmol) in anhydrous 1,4-dioxane (10ml) was evacuated and refilled with nitrogen (3 times) The reaction was heated under nitrogen at 95°C overnight before evaporating under reduced pressure. The residue was triturated with EtOAc (20ml), filtered and re-evaporated to give a gum. Chromatography on silica gel with MeOH DCM (2 98 to 5 95) gave the title compound as a yellow solid. (70 mg 15%) NMR. 1 39 (d, 6H), 2 47 (s, 3H), 2 92 (s, 3H), 3 17 (m, 4H), 3 26 (m, 4H), 5 70 (septuplet, 1H), 6 92 (d, 2H), 6 94 (d, 1H), 7 39 (s, 1H), 7 48 (d, 2H), 8 32 (d, 1H), 9 18 (s, 1H), m/z 456

Example 2

2-[4-(4-Mesylpiperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl 1*H*-imidazol-5-yl)-5-chloropyrimidine

The title compound was prepared according to the procedure of Example 1 using 2-amino-5-chloro-4-(1-isopropyl-2-methyl-1*H* imidazol-5-yl)pyrimidine (Method 5) heating for 30 hours at 100°C Chromatography on silica gel with MeOH DCM (2 98 to 6 94) NMR 1 36 (d, 6H), 2 46 (s, 3H), 2 80 (s, 3H), 3 16 (m, 4H), 3 23 (m, 4H), 4 79 (septuplet, 1H), 6 91 (d, 2H), 7 22 (s, 1H), 7 49 (d, 2H), 8 51 (d, 1H), 9 49 (s, 1H), m/z 490

48

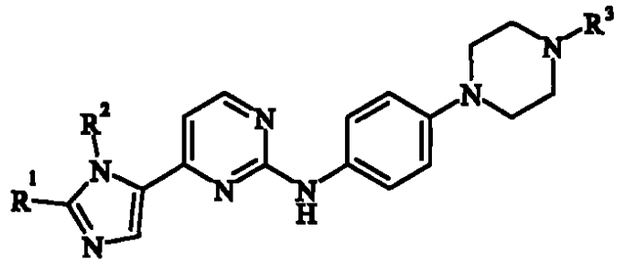
Example 3

2-[4-(4-Mesylpiperazin 1-yl)anilino]-4-(1-cyclobutyl-2-methyl-1*H* imidazol-5 yl)pyrimidine

5-(3-Dimethylaminoprop-2-en 1-oyl) 1-cyclobutyl-2-methylimidazole (Method 37 of WO 03/076435, 233 mg 1 mmol) and N-{4-[4-(methylsulphonyl)piperazin 1-yl]phenyl} guanidine (Method 1, 390 mg 1 3mmol) in 2 methoxyethanol (8 ml) was stirred and heated for 18 hours at 110°C The reaction mixture was evaporated under reduced pressure and the residue purified by chromatography on silica gel with MeOH DCM (3 97 to 8 92) After evaporation and trituration with ether, the title compound was obtained as a yellow solid. (227 mg 48 5%) NMR 1 60 - 1 71 (2xm, 2H), 2 36 (m, 4H), 2 49 (s, 3H), 2 91 (s, 3H), 3 18 (m, 4H), 3 25 (m, 4H), 5 51 (quintet, 1H), 6 91 (d, 1H), 6 97 (d, 2H), 7 30 (s, 1H), 7 54 (d, 2H), 8.33 (d, 1H), 9.23 (s, 1H), m/z 468

Examples 4-17

The following compounds were prepared by the procedure of Example 3 using the appropriate imidazole and N {4-[4-(methylsulphonyl)piperazin-1-yl]phenyl}guanidine (Method 1) or *N*-[4-(4-acetylpiperazin 1 yl)phenyl]guanidine bicarbonate salt (Method 2)



Ex	R^1	R^2	R^3	NMR	m/z	SM
4[1]	Me	Cyclopropyl -methyl	$MeSO_2$	0 09 (m, 2H), 0 28 (m, 2H), 1 00 (m, 1H), 2 39 (s, 3H), 2 92 (s, 3H) 3 18 (m, 4H), 3.24 (m, 4H), 4 49 (d, 2H), 6 94 (d, 2H), 7 02 (d, 1H), 7 47 (d, 2H), 7 58 (s, 1H) 8 30 (d, 1H), 9 15 (s, 1H)	468	Meth 41 in WO 03/07643 5

Ex	R^1	R^2	R^3	NMR	m/z	SM
5[2]	Et	Et	$MeSO_2$	1 11 (t, 3H) 1 24 (t, 3H), 2 71 (q, 2H), 2 91 (s, 3H), 3 18 (m, 4H), 3 23 (m, 4H) 4 50 (q, 2H), 6 95 (d, 2H), 7 03 (d, 1H), 7 47 (d, 2H), 7 61 (s, 1H), 8 28 (d, 1H), 9 12 (s, 1H)	456	Meth 55 of WO 03/07643 4
6[3]	Et	*i*-Pr	$MeSO_2$	1 28 (t, 3H), 1 40 (d, 6H), 2 79 (q, 2H), 2 91 (s, 3H), 3 17 (m, 4H), 3 24 (m, 4H), 5 61 (septuplet, 1H), 6 93 (d, 2H), 6 94 (d, 1H), 7 40 (s, 1H), 7 49 (d, 2H), 8 32 (d, 1H) 9 18 (s, 1H)	470	Meth 9
7[4]	$MeOCH_2$-	*i*-Pr	$MeSO_2$-	1 42 (d, 6H), 2 92 (s, 3H), 3 17 (m, 4H), 3.24 (m, 4H), 3 27 (s, 3H), 4 53 (s, 2H), 5 52 (septuplet, 1H), 6 94 (d, 2H), 6 99 (d, 1H), 7 47 (s, 1H), 7 49 (d, 2H), 8 38 (d, 1H), 9 21 (s, 1H)	486	Meth 50 of WO 03/07643 4
8[5]	Pr	Et	$MeSO_2$	0 97 (t, 3H), 1 12 (t, 3H), 1 72 (sextuplet, 2H), 2 68 (t, 2H), 2 92 (s, 3H), 3 16 (m, 4H), 3.27 (m, 4H), 4 51 (q, 2H), 6 93 (d, 2H), 7 02 (d, 1H), 7 48 (d, 2H), 7 62 (s, 1H), 8 29 (d, 1H), 9 12 (s, 1H)	470	Meth 13

Ex	R^1	R^2	R^3	NMR	m/z	SM
9 [6]	Me	Et	$MeSO_2$-	1 12 (t, 3H), 2 38 (s, 3H), 2 91 (s, 3H), 3 17 (m, 4H), 3 24 (m, 4H) 4 50 (q, 2H) 6 94 (d, 2H), 7 02 (d, 1H), 7 48 (d, 2H), 7 60 (s, 1H), 8.29 (d, 1H), 9 13 (s, 1H)	442	Meth 16 of WO 02/20512
10 [7]	Me	*i*-Bu	$MeSO_2$-	0 60 (d, 6H), 1 69 (septuplet, 1H), 2 36 (s, 3H), 2 92 (s 3H), 3 16 (m, 4H), 3 25 (m, 4H), 4 32 (d, 2H), 6 94 (d, 2H), 7 01 (d, 1H), 7 47 (d, 2H), 7 58 (s, 1H), 8.29 (d, 1H), 9 18 (s, 1H)	470	Meth 29 of WO 03/076436
11 [8]	Et	*i* Pr	MeC(O)	1 28 (t, 3H), 1 40 (d, 6H), 2 02 (s, 3H), 2 79 (q, 2H), 3 00 (t, 2H), 3 08 (t, 2H), 3 57 (m, 4H), 5 60 (septuplet, 1H), 6 91 (d, 2H), 6 94 (d, 1H), 7 41 (s, 1H), 7 48 (d, 2H), 8 31 (d, 1H), 9 18 (s, 1H)	434	Meth 9
12	Pr	Et	MeC(O)-	0 95 (t, 3H), 1 10 (t, 3H), 1 70 (septuplet, 2H) 2 02 (s, 3H), 2 68 (t, 2H), 3 01 (t, 2H), 3 08 (t, 2H), 3 59 (q, 4H), 4 51 (q, 2H), 6 92 (d, 2H), 7 02 (d, 1H), 7 44 (d, 2H), 7 62 (s, 1H), 8.29 (d, 1H), 9 11 (s, 1H)	434	Meth 13

Ex	R^1	R^2	R^3	NMR	m/z	SM
13	Me	Cyclobutyl	MeC(O)-	1 60 (sextet, 1H), 1 73 (q, 1H), 2 05 (s, 3H), 2 30-2 48 (m, 4H), 3 031 (t, 2H), 3 09 (t, 2H), 3 59 (q, 4H), 5 58 (quintet, 1H), 6 93 (d, 1H), 6 96 (d, 2H), 7 32 (s, 1H), 7 57 (d, 2H), 8 34 (d, 1H), 9 24 (s, 1H)	432	Meth 37 of WO 03/076435
14	Et	Et	MeC(O)-	1 12 (t, 3H), 1 24 (t, 3H), 2 03 (s, 3H), 2 71 (q, 2H), 3 01 (t, 2H), 3 08 (t, 2H), 3 57 (q, 4H), 4 49 (q, 2H), 6 92 (d, 2H) 7 01 (d, 1H), 7 45 (d, 2H), 7 61 (s, 1H), 8 29 (d, 1H), 9 10 (s, 1H)	420	Meth 55 of WO 03/076434
15	Me	Et	MeC(O)-	1 11 (t, 3H), 2 03 (s, 3H), 2 38 (s, 3H), 3 02 (t, 2H), 3 08 (t, 2H), 3 57 (q, 4H), 4 50 (q, 2H), 6 92 (d, 2H), 7 01 (d, 1H), 7 46 (d, 2H), 7 59 (s, 1H), 8.28 (d, 1H), 9 09 (s, 1H)	406	Meth 16 of WO 02/20512
169	$MeOCH_2$-	*i*-Pr	MeC(O)-	1 42 (d, 6H), 2 03 (s, 3H), 3 01 (t, 2H), 3 08 (t, 2H), 3 27 (s, 3H), 3 57 (q, 4H), 4 53 (s, 2H), 5 52 (septuplet, 1H), 6 91 (d, 2H), 6 99 (d, 1H), 7 44 (s, 1H), 7 47 (d, 2H), 8 38 (d, 1H), 9 20 (s, 1H)	450	Meth 50 of WO 03/076434

Ex	R^1	R^2	R^3	NMR	m/z	SM
17 [10]	Me	i-Bu	MeC(O)	0 60 (d, 6H), 1 69 (septuplet, 1H), 2 02 (s, 3H), 2 35 (s, 3H), 2 99 (t, 2H), 3 07 (t, 2H), 3 58 (q, 4H), 4 33 (d, 2H), 6 93 (d, 2H), 7 00 (d, 1H), 7 45 (d, 2H), 7 58 (s, 1H), 8 28 (d, 1H), 9 13 (s, 1H)	434	Meth 29 of WO 03/07643 6

[1] This compound required further chromatography on neutral alumina (activity II) eluting with EtOAc.DCM (1 1) then EtOAc DCM (1 1) with 5%v/v MeOH The title compound was crystallised from MeOH (120 mg 25 6%)

[2] Chromatography with MeOH DCM (2 98 to 6 94) The title compound was crystallised from acetonitrile (149 mg 32 7%)

[3] Chromatography with MeOH DCM (3 97 to 5 95) (127 mg 27%)

[4] Chromatography with MeOH DCM (3 97) (180 mg 37%)

[5] Chromatography with MeOH DCM (2 98 to 6 94) (290 mg 34 5%)

[6] Chromatography with MeOH DCM (2 98 to 6 94) (340 mg 38 5%)

[7] Chromatography with MeOH.DCM (2 98 to 6 94) (350 mg 41 7%)

[8] 5-(3-Dimethylaminoprop-2-en-1-oyl)-1-isopropyl-2-ethylimidazole (Method 9, 470 mg 2 mmol) and N [4-(4-acetylpiperazin-1-yl)phenyl]guanidine bicarbonate salt (Method 2, 740 mg 2 3mmol) in 2 methoxyethanol (10 ml) was stirred and heated for 24 hours at 110°C The reaction mixture was evaporated under reduced pressure and the residue purified by chromatography on silica gel with MeOH DCM (2 98 to 6 94) After evaporation and trituration with ether, the title compound was obtained as a yellow solid. (290 mg 33 4%)

[9] Chromatography with MeOH.DCM (3 97 to 8 92) (186 mg 20 7%)

[10] Chromatography with MeOH DCM (2 98 to 6 94) (372 mg 40%)

Example 18

2-[4 (4-Acetylpiperazin-1-yl)anilino]-4-(1-isopropyl 2-methyl-1*H* imidazol-5 yl)pyrimidine

(2*E*)-3-(Dimethylamino)-1-(1 isopropyl-2-methyl-1*H* imidazol-5-yl)prop-2-en-1-one (Method 24 of WO 03/076436, 140 mg 0 63 mmol) and N-[4-(4-acetylpiperazin-1-yl)phenyl]guanidine bicarbonate salt (Method 2, 240 mg 0 74 mmol) in 2-methoxyethanol (4

ml) were reacted under nitrogen under microwave conditions at 200°C for 30 minutes. After evaporation under reduced pressure, chromatography on silica gel with MeOH DCM (2 98 to 6 94) gave the title compound, after ether trituration, as a yellow solid. (85 mg 31 5%) NMR 1 39 (d, 6H), 2 02 (s, 3H), 2 45 (s, 3H), 3 00 (b t, 2H), 3 06 (b t, 2H), 3 56 (b q, 4H), 5 70 (septuplet, 1H) 6 91 (d, 2H), 6 95 (d, 1H) 7 38 (s, 1H), 7 46 (d, 2H), 8 31 (d, 1H) 9 15 (s, 1H), m/z 420

Example 19

2-[4-(4-Acetylpiperazin-1-yl)anilino]-4-[1-(cyclopropylmethyl)-2-methyl-1*H*-imidazol-5-yl]pyrimidine

The title compound was prepared by the procedure of Example 18 from 5 (3 dimethylaminoprop-2-en-1-oyl)-1-cyclopropylmethyl 2-methylimidazole (Method 41 in WO 03/076435) except that the reaction was heated in microwave at 200°C for 40 minutes 148 mg 53 4% NMR. 0 10 (m, 2H), 0 28 (m, 2H), 1 02 (m, 1H), 2 03 (s, 3H), 2 38 (s, 3H), 3 01 (t, 2H), 3 08 (t, 2H), 3 57 (q, 4H), 4 48 (d, 2H), 6 92 (d, 2H), 7 01 (d, 1H), 7 43 (d, 2H), 7 57 (s, 1H), 8 281 (d, 1H), 9 12 (s, 1H), m/z 432

Example 20

2-[4-(Piperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl 1*H* imidazol-5-yl)pyrimidine

2-[4-(4-Acetylpiperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl 1*H*-imidazol-5-yl)pyrimidine (Example 18, 1 3g) was stirred and heated in isopropanol (15ml) and 33% hydrochloric acid (1 5ml) at 90°C for 4 5 hours The reaction was evaporated under reduced pressure and then basified with 7N ammonia in MeOH and re-evaporated. Toluene was added and the mixture was re-evaporated (3 times) The residue was purified by chromatography on neutral alumina, activity II eluting with MeOH DCM (5 95) to give the title compound as a yellow gum (330 mg 28%) NMR. 1 40 (d, 6H) 2 46 (s, 3H), 2 82 (m, 4H), 2 96 (m, 4H) 5 69 (septuplet, 1H), 6 85 (d, 2H), 6 93 (d, 1H), 7 18 (s, 1H), 7 42 (d, 2H), 8 30 (d, 1H), 9 11 (s, 1H), m/z 378

Example 21

2-{4-[4-(2-Acetoxyacetyl)piperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine

2-[4-(Piperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine (Example 20, 330mg 0.88 mmol) was stirred in DCM (6ml) at room temperature. Triethylamine was added (153mg 1.51 mmol) followed by dropwise addition of acetoxyacetylchloride (143 mg 1.05 mmol). After stirring for 1.25 hours, DCM (10 ml) and brine (5 ml) were added. The reaction was stirred vigorously for 10 minutes then the organic layers were separated, dried and evaporated under reduced pressure to give the title compound as a yellow foam. Quantitative yield. The solid was triturated with ether and re-evaporated. NMR. 1.40 (d, 6H), 2.08 (s, 3H), 2.48 (s, 3H), 3.05 (b d, 4H), 3.54 (b d, 4H), 4.81 (s, 2H), 5.70 (septuplet, 1H), 6.92 (d, 2H), 6.95 (d, 1H), 7.40 (s, 1H), 7.48 (d, 2H), 8.31 (d, 1H), 9.18 (s, 1H), m/z 478

Example 22

2-{4-[4-(2-Hydroxyacetyl)piperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine

2-{4-[4-(2-Acetoxyacetyl)piperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine (Example 21 330mg) was stirred in MeOH (5 ml) at room temperature and 7N ammonia in MeOH (1.6 ml) was added. After 28 hours, the reaction was evaporated under reduced pressure. Chromatography on silica gel using MeOH:DCM (4.96 to 5.95), yielded the title compound as a yellow solid. (108 mg 36%). NMR. 1.39 (d, 6H), 2.46 (s, 3H), 3.05 (b s, 4H), 3.48 (b s, 2H), 3.61 (b s, 2H), 4.12 (d, 2H), 4.57 (t, 1H), 5.69 (septuplet, 1H), 6.92 (d, 2H), 6.95 (d, 1H), 7.38 (s, 1H), 7.47 (d, 2H), 8.31 (d, 1H), 9.15 (s, 1H), m/z 436

Example 23

2-{4-[4-(2-Dimethylaminoacetyl)piperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine

Chloroacetyl chloride (50µl, 0.65 mmol) was added dropwise to a stirred solution of 2-[4-(piperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine (Example 20, 200 mg, 0.53 mmol) and triethylamine (90 µl, 0.65 mmol) in DCM (5 ml) at room temperature. After 50 minutes, 2M dimethylamine in THF solution (2 ml, 4mmol) was added

and the reaction was stirred for 5 hours before evaporating under reduced pressure. Chromatography on neutral alumina (activity II) with MeOH DCM (1 99 to 3 97) gave material which required further purification on silica gel with MeOH DCM 7N NH_3 MeOH (3 97 0025 to 10 90 0025) to give the title compound as a yellow foam. (150 mg 60% yield) NMR. 1 39 (d, 6H), 2 19 (s, 6H), 2 46 (s, 3H), 3 02 (b t, 2H), 3 06 (b t, 2H), 3 59 (b t, 2H), 3 68 (b t, 2H), 5 69 (septuplet, 1H), 6 92 (d, 2H), 6 94 (d, 1H), 7.39 (s, 1H), 7 47 (d, 2H), 8 31 (d, 1H) 9 17 (s, 1H), m/z 463

Example 24

2-{4-[4-(Chloroacetyl)piperazin-1 yl]anilino}-4-(1 isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine

2-[4-(Piperazin-1-yl)anilino]-4-(1 isopropyl-2 methyl-1*H* imidazol 5 yl)pyrimidine (Example 20,1 89g, 5 mmol) di-isopropylethylamine (0 956 ml, 5 5 mmol) in DCM (25 ml) was treated at 0°C with chloroacetyl chloride (0 438 ml, 5 5 mmol) The mixture was stirred at ambient for 2 hours, diluted with DCM (25 ml), washed with aqueous saturated sodium bicarbonate solution (20 ml) and aqueous saturated sodium chloride solution (20 ml) The solution was dried and evaporated at reduced pressure to give the title compound, (1 96g, 87%) NMR ($CDCl_3$) 8 30 (d, 1H), 7 44 (d, 2H), 7 35 (s, 1H), 6 96 (s, 1H), 6 92 (d, 1H), 6 85 (d, 1H), 5 68 – 5 56 (m, 1H), 4 12 (s 2H), 3 83 – 3 76 (m, 2H), 3 72 – 3 67 (m, 2H) 3 22 – 3 11 (m, 4H), 2 59 (s, 3H), 1 48 (d, 6H), m/z 454

Example 25

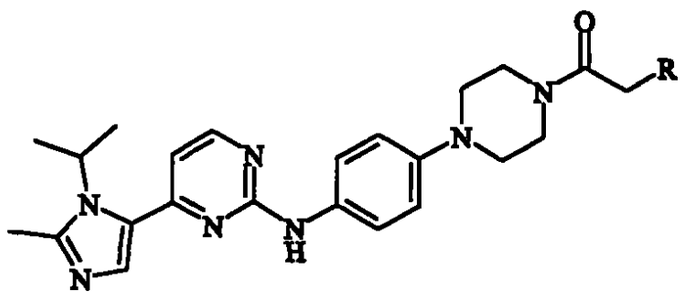
2 {4-[4-(Azetidin-1 ylacetyl)piperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5 yl)pyrimidine hydrochloride

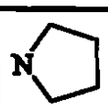
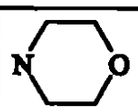
2-{4-[4-(Chloroacetyl)piperazin-1-yl]anilino}-4-(1-isopropyl 2-methyl-1*H*-imidazol-5-yl)pyrimidine (Example 24, 0 34g, 0 75mmol) and azetidine (2ml) was stirred for 24 hours at ambient temperature The solution was diluted with EtOAc (20ml), washed with aqueous saturated sodium bicarbonate solution (10 ml) and aqueous saturated sodium chloride solution (10 ml), then dried and evaporated at reduced pressure The residue was purified by chromatography on a 40g silica column, eluted with a 3% MeOH – ammonia/DCM to 5% MeOH – ammonia/DCM gradient, to give the amine, which was converted to the hydrochloride salt by dissolving in EtOAc (3 ml) and treating with a 1 0 molar solution of ethereal-HCl (0 75 ml) The solid was triturated with ether (20 ml) and filtered to give the title

compound(24mg, 7%) NMR 9 77 (s, 1H), 8 58 (d, 1H) 8 20 (s, 1H), 7 61 (d, 2H), 7 35 - 7 24 (m, 2H), 7 13 (d, 1H), 5 64 5 55 (m, 1H) 4 65 (brs, 1H), 4 44 (d, 2H), 4.23 - 4 11 (m, 2H), 4 09 - 3 96 (m, 2H), 3 81 - 3 71 (m, 2H), 3 69 - 3 59 (m, 2H), 3 42 - 3 31 (m, 2H), 3 30 3 17 (m, 2H), 2 48 – 2 24 (m, 2H), 2 81 (s, 3H), 1 48 (d, 6H) m/z 475

Examples 26-28

The following salts were prepared using the procedure of Example 25 from 2-{4-[4-(chloroacetyl)piperazin-1 yl]anilino}-4-(1 isopropyl-2-methyl-1*H* imidazol 5 yl)pyrimidine Example 24) and the appropriate amine



Ex	R	NMR	m/z	Salt
26		10 29 (brs, 1H), 9 91 (s, 1H), 8 60 (d, 1H), 8.23 (s, 1H), 7 68 (d, 2H), 7 53 7 42 (m, 2H), 7 17 (d, 1H), 5 65 - 5 56 (m, 1H), 4 48 (d, 2H), 3 94 (s, 2H), 3 80 (s, 2H), 3 64 - 3 53 (m, 2H), 3 51 (s, 2H), 3 41 - 3 31 (m, 2H), 3 18 - 3 02 (m, 2H) 2 83 (s, 3H), 2 06 - 1 84 (m, 4H), 1 49 (d, 6H)	489	HCl
27		9 90 (s, 1H), 8 60 (d, 1H), 8 22 (s, 1H), 7 66 (d, 2H), 7 48 - 7 37 (m, 2H), 7 16 (d, 1H), 5 65 - 5 55 (m, 1H), 4 99 (s, 2H), 4 53 (s, 1H), 4 01 - 3 70 (m, 8H), 3 51 - 3 41 (m, 4H) 3 38 3 31 (m, 2H), 3 27 - 3 12 (m, 2H), 2.82 (s, 3H), 1 49 (d, 6H)	505	HCl
28	$N(Et)_2$	9 98 (s, 1H), 9 57 (s, 1H), 8 61 (d, 1H), 8 23 (s, 1H), 7 71 (d, 2H), 7 52 (d, 2H), 7 18 (d, 1H), 5 65 5 56 (m, 1H), 4 38 (d, 2H), 3 98 - 3 78 (m, 4H), 3 55 - 3 37 (m, 4H), 3 24 - 3 12 (m, 4H), 2 83 (s, 3H), 1 50 (d, 6H), 1.24 (t, 6H)	491	HCl

Example 29

2-{4-[4-(Vinylsulphonyl)piperazin 1 yl]anilino}-4-(1-isopropyl-2 methyl-1*H* imidazol 5 yl)pyrimidine

2-[4-(Piperazin-1-yl)anilino]-4-(1 isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine (Example 20, 370mg 0 98 mmol) was stirred in DCM (10 ml) at room temperature Triethylamine (150mg 1 49 mmol) was added followed by dropwise addition of 2-chloro-1-ethanesulphonyl chloride (196 mg 1 2 mmol) in DCM (1 ml) After stirring for 1 25 hours, the reaction was evaporated under reduced pressure and triturated with ether The resulting solid was treated with water (15 ml) the basified with saturated sodium hydrogen carbonate solution and extracted into DCM (2x20 ml) The organics were washed with brine (10 ml), dried and evaporated to give a gum. After chromatography on silica gel using MeOH DCM (3 97 to 5 95) the title compound was obtained as a yellow solid (140 mg 30 4%) NMR 1 39 (d, 6H), 2 46 (s, 3H), 3 16 (s, 8H), 5 68 (septuplet, 1H), 6 20 (d, 1H), 6 85 (dd, 1H), 6 91 (d, 2H), 6 95 (d, 1H), 7 38 (s, 1H), 7 47 (d, 2H), 8 30 (d, 1H), 9 16 (s, 1H), m/z 468

Example 30

2 {4-[4-(2-Dimethylaminoethylsulphonyl)piperazin 1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H* imidazol-5-yl)pyrimidine

Dimethylamine (2 0M) in THF (1 5 ml) was added to a stirred suspension of 2-{4-[4-(vinylsulphonyl)piperazin 1-yl]anilino}-4-(1-isopropyl 2-methyl-1*H* imidazol-5-yl) pyrimidine (Example 29, 140 mg 0 3 mmol) in THF (3 ml) at room temperature. Additional dimethylamine solution (0 5 ml) was added after 2 hours The reaction was stirred for 1 hour then stood overnight. The reaction was evaporated under reduced pressure, triturated with ether and filtered to give the title compound as a yellow solid. (134mg 89%) NMR. 1 40 (d, 6H), 2 46 (s, 3H), 2 62 (t, 2H), 3 13 (t, 4H), 3 20-3 35 (2H and 4H)[under exchangeables], 5 68 (septuplet, 1H), 6 92 (d, 2H) 6 95 (d, 1H), 7 38 (s, 1H), 7 47 (d, 2H), 8 31 (d, 1H), 9 18 (s, 1H) [+duetero acetic acid. 3 01 (b d, 2H), 3 14 (t, 4H), 3 33 (t, 4H), 3 37 (m, 2H)] m/z 478

Example 31

2-{4-[4-(2-Methoxyethylsulphonyl)piperazin 1-yl]anilino}-4-(1 isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine

Sodium methoxide (40 mg 0 74 mmol) was added to 2-{4-[4-(vinylsulphonyl) piperazin 1-yl]anilino}-4-(1-isopropyl-2 methyl 1*H*-imidazol-5-yl) pyrimidine (Example 29,300 mg 0 64 mmol) in MeOH (4 ml) After stirring at room temperature for 5 hours, the reaction was evaporated. After chromatography on silica gel using MeOH DCM EtOAc (5 47 5 47 5) and trituration with ether, the title compound was obtained as a yellow solid. NMR. 1 41 (d, 6H), 2 47 (s, 3H), 3 13 (m, 4H), 3 26 (4H alongside exchangeables), 3 37 (t, 2H), 3 67 (t, 2H), 5 69 (septuplet, 1H), 6 93 (d, 2H), 6 96 (d, 1H) 7 39 (s, 1H), 7 49 (d, 2H), 8 32 (d, 1H), 9 18 (s, 1H), m/z 500

Example 32

2 {4-[4-(2 Hydroxyethylsulphonyl)piperazin-1 yl]anilino}-4-(1 isopropyl-2-methyl-1*H* imidazol 5-yl)pyrimidine

A mixture of 2-{4-[4-(vinylsulphonyl)piperazin-1 yl]anilino}-4-(1 isopropyl-2-methyl-1*H*-imidazol 5 yl) pyrimidine (Example 29,260 mg 0 56 mmol) and barium hydroxide (560 mg 3 27 mmol) in water (10 ml) was heated at 65°C 90°C over 6 hours 1,4-dioxane (1 ml) was added after 1, 2, 3 and 5 hours After evaporation under reduced pressure, the residue was treated with water (10 ml) and saturated sodium hydrogen carbonate solution (10 ml) The suspension was extracted with DCM (30 ml and 2x20 ml) and EtOAc (25 ml) Both extracts were washed (separately) with brine (10 ml) and dried (Na_2SO_4) The extracts were combined and evaporated. After chromatography on silica gel using MeOH DCM (4 96 to 8 92), the title compound was obtained as a yellow solid (108 mg 40%) NMR. 1 40 (d, 6H), 2 49 (s, 3H), 3 13 (m, 4H), 3 23 (t, 2H), 3 30 (m, 4H), 3 76 (q, 2H), 5 01 (t, 1H), 5 69 (septuplet, 1H), 6 93 (d, 2H), 6 96 (d, 1H), 7 39 (s, 1H), 7 48 (d, 2H), 8 31 (d, 1H), 9 18 (s, 1H), m/z 486

Example 33

2-[4-(4-Acetylpiperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)-5-chloropyrimidine

(2*E*)-2-Chloro-3-(dimethylamino) 1-(1 isopropyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one (1 68g from Method 3 - assumed 5mmol) and *N*-[4-(4-acetylpiperazin-1-

yl)phenyl]guanidine bicarbonate salt (Method 2) (1 94g 6mmol) in 2-methoxyethanol (25ml) were heated under nitrogen at 110°C for 3 5 hours before evaporation under reduced pressure The residue was purified by chromatography on silica gel with MeOH.DCM (3 97 to 5 95) to give the title compound, after trituration with ether, as a foam. NMR. 1 36 (d, 6H), 2 02 (s, 3H), 2 48 (s, 3H), 3 00 (b t, 2H), 3 08 (b t, 2H), 3 56 (b q, 4H), 4 80 (septuplet, 1H), 6 90 (d, 2H), 7 21 (s, 1H), 7 47 (d, 2H), 8 50 (s, 1H), 9 48 (s, 1H), m/z 454

Example 34

2-[4-(Piperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl) 5-chloropyrimidine

The title compound was prepared from 2-[4-(4-acetylpiperazin-1-yl)anilino]-4-(1 isopropyl 2-methyl-1*H*-imidazol-5-yl) 5-chloropyrimidine (Example 33, 800mg) by the method of Example 20 Except that after purification by chromatography on neutral alumina, activity II eluting with MeOH.DCM (3 97) the title compound was isolated as a yellow gum. Trituration with ether gave a foam (50mg 7%) NMR. 1 34 (d, 6H), 2 45 (s, 3H), 2 82 (m, 4H), 2 96 (m, 4H), 4 82 (septuplet, 1H), 6 85 (d, 2H), 7 41 (s, 1H), 7 42 (d, 2H), 8 49 (s, 1H), 9 43 (s, 1H), m/z 412

Example 35

2-{4-[4-(Acetoxyacetyl)piperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol 5-yl)-5-chloropyrimidine

The title compound was prepared using the procedure of Example 21 using 400mg 0 97 mmol of 2-[4-(piperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl-1*H* imidazol-5-yl)-5-chloropyrimidine (Example 34) After work up, the mixture was purified by chromatography on silica gel using MeOH DCM (3 97 to 6 94) to give a solid (230 mg) NMR. 1 35 (d, 6H), 2 08 (s, 3H), 2 48 (s, 3H), 3 04 (b d, 4H), 3 52 (b d, 4H), 4 80 (septuplet, 1H), 4 81 (s, 2H), 6 92 (d, 2H), 7.22 (s, 1H), 7 48 (d, 2H) 8 51 (d, 1H), 9 49 (s, 1H), m/z 512

Example 36

2-{4-[4-(Hydroxyacetyl)piperazin-1-yl]anilino}-4-(1 isopropyl-2-methyl-1*H*-imidazol-5 yl)-5-chloropyrimidine

2-{4-[4-(Acetoxyacetyl)piperazin 1 yl]anilino}-4-(1 isopropyl-2-methyl-1*H*-imidazol-5-yl)-5-chloropyrimidine (Example 35) was deprotected by the procedure of Example 22 The reaction mixture was evaporated under reduced pressure The residue was

dissolved in DCM (30 ml), washed with water(15ml) and brine (15ml), dried and evaporated. The residue was triturated with ether and re-evaporated to give the title compound as a solid (180 mg) NMR. 1 34 (d, 6H), 2 48 (s, 3H), 3 03 (b s, 4H), 3 52 (b d, 4H), 4 11 (d, 2H), 4 59 (t, 1H), 4 80 (septuplet, 1H), 6 91 (d, 2H), 7 21 (s, 1H) 7 47 (d, 2H) 8 51 (s, 1H), 9 49 (s, 1H), m/z 470

Example 37

2-{4-[4-(2-Hydroxy-2-methylpropionyl)piperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl 1*H*-imidazol 5 yl)-5-chloropyrimidine

2-Hydroxyisobutyric acid (162 mg. 1 mmol) was added to a solution of 1 1'-carbonyldiimidazole (162 mg. 1 mmol) in DCM (4 ml) and stirred at room temperature for 15 minutes A solution of 2-[4-(piperazin 1 yl)anilino]-4-(1 isopropyl-2-methyl-1*H*-imidazol 5-yl)-5-chloropyrimidine (Example 34 400 mg. 0 97 mmol) in DCM (8 ml) was added and stirring continued for 19 hours DCM (25 ml) was added and the organic layer was washed with 5% (v/v) acetic acid (15 ml), water (15 ml), brine (15 ml) and dried before evaporating under reduced pressure Chromatography on silica gel with MeOH DCM (4 96 to 8 92) gave the title compound, after ether trituration, as a solid. (67 mg 14%) NMR. (500MHz) 1 30 (d, 6H), 1 34 (d, 6H), 2 48 (s, 3H), 3 04 (t, 4H), 3 62 (b s, 4H), 4 00 (b s 4H), 4 79 (septuplet, 1H), 5 41 (s, 1H), 6 90 (d, 2H), 7 22 (s, 1H), 7 48 (d, 2H), 8 51 (s, 1H), 9 49 (s, 1H), m/z 498

Example 38

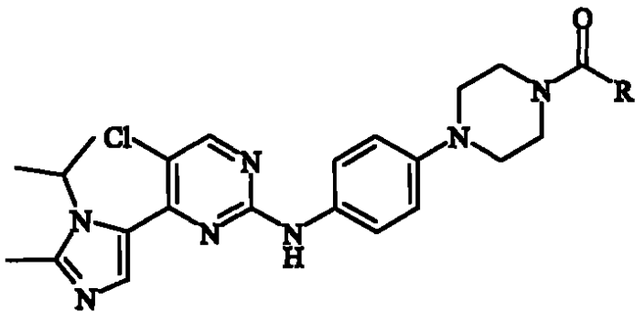
2-{4-[4-(2-(S)-2-Hydroxypropionyl)piperazin-1-yl]anilino}-4-(1 isopropyl-2-methyl-1*H*-imidazol 5-yl) 5-chloropyrimidine

To a solution of 2-[4-(piperazin 1 yl)anilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol 5-yl)-5-chloropyrimidine (Example 34 276mg, 1 00mmol) in DMF (7ml) was added L-lactic acid (90mg, 1 50mmol), and DIPEA (245µl, 181mg, 2 1mmol) A solution of HATU (330mg, 1 30mmol) in DMF (3ml) was added drop wise, then the mixture was stirred at ambient temperature for 20 hours The solution was concentrated *in vacuo* then the residue dissolved in EtOAc (20ml), and washed with aqueous sodium bicarbonate solution (15ml) then brine (15ml) The organic extract was dried and concentrated. The residue was purified by chromatography on silica gel with 2N NH_3-MeOH DCM (3 97 to 5 95) to yield the title compound as a white solid (233mg, 72%) NMR. 1 37 (d, 3H) 1 45 (d, 6H), 2 58 (s, 3H),

3 12-3 17 (m, 4H), 3 56-3 60 (m, 2H), 3 75 3 92 (m, 3H), 4 48-4 54 (m, 1H), 4 96 (quintet, 1H), 6 91 (d, 2H), 6 94 (s, 1H), 7 43 (d, 2H) 7 50 (s, 1H) 8 38 (s, 1H), m/z 484

Examples 39-47

The following compounds were prepared by the procedure of Example 38 using the appropriate acid and 2-[4-(piperazin-1-yl)anilino]-4-(1 isopropyl-2-methyl-1*H*-imidazol-5-yl)-5-chloropyrimidine (Example 34)

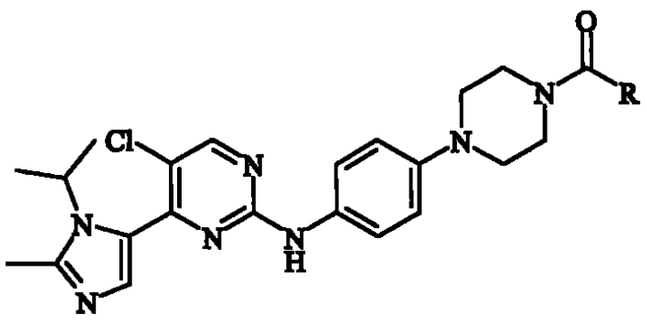


Ex	R	NMR (300MHz, $CDCl_3$)	m/z
39	(*R*)-MeCH(OH)-	1 37 (d, 3H), 1 45 (d, 6H), 2 58 (s, 3H), 3 12-3 17 (m, 4H), 3 56-3 60 (m, 2H), 3 75-3 92 (m, 3H), 4 48-4 54 (m, 1H), 4 96 (quintet, 1H), 6 91 (d, 2H), 6 94 (s, 1H), 7 43 (d, 2H), 7 50 (s, 1H), 8 38 (s, 1H)	484
40	$MeOCH_2$-	1 43 (d, 6H) 2 57 (s, 3H), 3 10-3 15 (m, 4H), 3 44 (s, 3H), 3 65-3 69 (m, 2H), 3 76-3 80 (m, 2H), 4 15 (s, 2H), 4 93 (quintet, 1H), 6 91 (d, 2H), 6 94 (s, 1H), 7 41 (d, 2H), 7 50 (s, 1H), 8 37 (s, 1H)	484
41	1-Hydroxycycloprop-1-yl	(d6-DMSO) 0 74-0 78 (m, 2H), 0 90-0 95 (m, 2H), 1 34 (d, 6H), 2 46 (s, 3H), 3 04-3 08 (m, 4H), 3 68-3 80 (m, 4H), 4 79 (quintet, 1H), 6 33 (s, 1H), 6 91 (d, 2H), 7 21 (s, 1H), 7 45, (d, 2H), 8 50 (s, 1H), 9 48 (s, 1H)	496
42	(*R*)-MeCH(OMe)-	1 42-1 46 (m, 9H), 2 58 (s, 3H), 3 11-3 16 (m, 4H), 3 37 (s, 3H), 3 78-3 86 (m, 4H), 4 20 (q, 1H), 4 94 (quintet, 1H), 6 91 (d, 2H), 6 93 (s, 1H), 7 42 (d, 2H), 7 51 (s, 1H), 8 38 (s, 1H)	498

Ex	R	NMR (300MHz, $CDCl_3$)	m/z
43	(*S*)-MeCH(OMe)-	1 42-1 46 (m, 9H), 2 58 (s, 3H), 3 11-3 16 (m, 4H), 3 37 (s, 3H), 3 78-3 86 (m, 4H), 4 20 (q, 1H), 4 94 (quintet, 1H), 6 91 (d, 2H), 6 93 (s 1H), 7 42 (d, 2H), 7 51 (s, 1H), 8 38 (s, 1H)	498
44	(*S*)-$MeCH_2CH(OH)$-	1 01 (t, 3H), 1 43 (d, 6H), 1 49 1 58 (m, 1H), 1 69-1 78 (m, 1H), 2 57 (s, 3H), 3 11-3 15 (m, 4H), 3 55-3 59 (m, 2H), 3 70-3 90 (m, 3H), 4 34-4 38 (m, 1H), 4 92 (quintet, 1H), 6.91 (d, 2H), 6 96 (s, 1H), 7 42 (d, 2H), 7 51 (s, 1H), 8 37 (s, 1H)	498
45	MeCH(Me)-	1 17 (d, 6H), 1 44 (d, 6H), 2 58 (s, 3H), 2 82-2 89 (m, 1H), 3 09 3 15 (m, 4H), 3 66-3 72 (m, 2H), 3 76-3 82 (m, 2H), 4 94 (quintet, 1H), 6 91 (d, 2H), 6 93 (s, 1H), 7 41 (d, 2H), 7 51 (s, 1H), 8 38 (s, 1H)	482
46	Cyclopropyl	0 77-0 83 (m, 2H), 1 00-1 05 (m, 2H), 1 44 (d, 6H), 1 74-1 81 (m, 1H), 2 58 (s, 3H), 3 11 3 19 (m, 4H), 3 79-3 87 (m, 4H), 4 94 (quintet, 1H), 6 91 (d, 2H), 6 94 (s, 1H), 7 41 (d, 2H), 7 51 (s, 1H) 8 37 (s, 1H)	480
47	(*R*)-$MeCH_2CH(OH)$	1 01 (t, 3H), 1 43 (d, 6H), 1 49-1 58 (m, 1H), 1 69 1 78 (m, 1H), 2 57 (s, 3H), 3 11-3 15 (m, 4H), 3 55-3 59 (m, 2H), 3 70-3 90 (m, 3H), 4 34-4 38 (m, 1H), 4 92 (quintet, 1H), 6 91 (d, 2H), 6 96 (s, 1H), 7 42 (d, 2H), 7 51 (s 1H), 8 37 (s, 1H)	498

Examples 48-64

The following compounds were prepared by the procedure of Example 38 using the appropriate acid and 2-[4-(piperazin-1 yl)anilino]-4-(1 isopropyl-2-methyl-1*H*-imidazol 5-yl) 5-chloropyrimidine (Example 34) The isolated free bases were then dissolved in EtOAc (3ml) with the addition of a few drops of MeOH to aid dissolution. 1 0M hydrogen chloride in ether solution (1equivalent) was added, and the resultant hydrochloride salts were triturated with ether then filtered and dried *in vacuo*



Ex	R	NMR	m/z
48	$MeOCH_2CH_2$-	1 42 (d, 6H) 2 48 (s, 3H), 2 63 (t, 2H), 2 79 (s, 3H), 3 23-3 30 (m, 4H), 3 57 (t, 2H), 3 77 3 82 (m, 4H), 4 80 (quintet, 1H), 7 34-7 38 (m, 2H), 7 62 (d, 2H), 7 99 (s, 1H), 8 76 (s, 1H), 10 08 (brs, 1H)	498
49	1-Cyanocycloprop-1-yl-	1 42 (d, 6H) 1 52-1 56 (m, 2H), 1 60-1 64 (m, 2H), 2 78 (s, 3H), 3 27-3 33 (m, 4H), 3 85-3 91 (m, 4H), 4 80 (quintet, 1H), 7.24 (d, 2H), 7 59 (d, 2H), 7 98 (s, 1H) 8 74 (s 1H) 10 01 (brs 1H)	505
50	(*R*)-Tetrahydrofur-2-yl-	1 42 (d, 6H), 1 79-1 87 (m, 2H), 1 98-2 11 (m, 2H), 2 78 (s, 3H), 3 19-3 27 (m, 4H), 3 70-3 83 (m, 6H), 4 70 (dd, 1H), 4 80 (quintet, 1H), 7.23-7 30 (m, 2H), 7 59 (d, 2H), 7 98 (s 1H), 8 74 (s, 1H), 10 02 (brs, 1H)	510
51	(*S*)-Tetrahydrofur-2-yl-	1 42 (d, 6H), 1 79-1 87 (m, 2H), 1 98-2 11 (m, 2H), 2 78 (s, 3H), 3 19-3 27 (m, 4H), 3 70-3 83 (m, 6H), 4 70 (dd, 1H), 4 80 (quintet, 1H), 7 23-7 30 (m, 2H), 7 59 (d, 2H) 7 98 (s, 1H), 8 74 (s, 1H) 10 02 (brs, 1H)	510
52	$MeC(Me)(OH)CH_2$-	1 19 (s, 6H), 1 42 (d, 6H), 2 50 (s, 2H), 2 79 (s, 3H), 3.25-3 33 (m, 4H), 3 81-3 89 (m, 4H), 4 80 (quintet, 1H), 7 34-7 40 (m, 2H) 7 63 (d, 2H) 7 99 (s, 1H), 8 76 (s, 1H), 10 08 (brs, 1H)	512

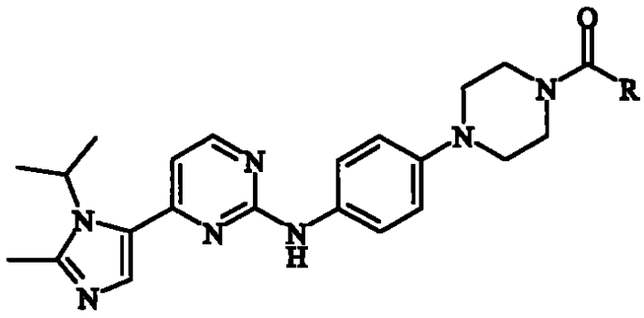
Ex	R	NMR	m/z
53	$HOCH_2C(Me)_2$-	1 18 (s 6H), 1 42 (d, 6H), 2 79 (s, 3H), 3 25-3 29 (m, 4H), 3 44 (s, 2H) 3 84-3 90 (m, 4H), 4 80 (quintet, 1H) 7 32-7 40 (m, 2H), 7 62 (d, 2H), 7 99 (s, 1H), 8 76 (s, 1H), 10 07 (brs, 1H)	512
54	(*R*)-MeCH(Me)CH(OH)-	0 84 (d, 3H), 0 88 (d, 3H), 1 42 (d, 6H), 1 82-1 90 (m, 1H), 2 79 (s, 3H), 3 27-3 33 (m, 4H), 3 85-3 92 (m, 4H), 4 06 (d, 1H), 4 79 (quintet, 1H) 7 38 7 42 (m, 2H), 7 64 (d, 2H), 7 99 (s, 1H), 8 76 (s, 1H) 10 09 (brs, 1H)	512
55	(*S*)-MeCH(Me)CH(OH)-	0 84 (d, 3H), 0 88 (d, 3H), 1 42 (d, 6H) 1 82-1 90 (m, 1H), 2 79 (s, 3H), 3 27-3 33 (m, 4H), 3 85 3 92 (m, 4H), 4 06 (d, 1H), 4 79 (quintet, 1H) 7 38 7 42 (m, 2H), 7 64 (d, 2H), 7 99 (s, 1H), 8 76 (s, 1H), 10 09 (brs, 1H)	512
56	$HC{\equiv}CCH_2OCH_2$-	1 42 (d, 6H), 2 78 (s, 3H), 3 22-3 30 (m, 4H), 3 49 (t, 1H), 3 67-3 75 (m, 4H), 4.23 (d, 2H), 4.26 (s, 2H), 4 80 (quintet, 1H), 7 26-7 33 (m, 2H), 7 61 (d, 2H), 7 99 (s, 1H), 8 75 (s, 1H), 10 04 (brs, 1H)	508
57	Tetrahydrofur-3-yl-	1 42 (d, 6H), 2 03 (q, 2H), 2 78 (s, 3H), 3.22-3 30 (m, 4H), 3 36-3 45 (m, 1H), 3 66-3 76 (m, 4H), 3 77 3 84 (m, 4H), 4 80 (quintet, 1H), 7.28-7 36 (m, 2H), 7 61 (d, 2H), 7 99 (s, 1H), 8 75 (s, 1H), 10 05 (brs, 1H)	510
58	$(Me)_2NCH_2CH_2$	1 42 (d, 6H), 2 74-2 78 (m, 9H), 2 93 (t, 2H), 3.21-3 32 (m, 6H), 3 72-3 78 (m, 4H) 4 80 (quintet, 1H), 7 22 7 28 (m, 2H), 7 59 (d, 2H), 7 99 (s, 1H), 8 74 (s, 1H), 10 01 (brs, 1H)	511

Ex	R	NMR	m/z
59	$HOCH_2N(Me)CH_2$-	1 42 (d, 6H), 2 78 (s 3H), 2 88-2 95 (7H, m), 3 20-3 31 (m, 4H), 3 42-3 51 (m, 4H), 4 80 (quintet, 1H), 7 05 (d, 2H) 7 52 (d, 2H) 7 98 (s, 1H), 8 71 (s, 1H), 9 89 (brs, 1H)	511
60	$(HOCH_2)_2C$-	1 42 (d, 6H), 2 78 (s, 3H), 3 05-3 11 (m, 1H), 3 22-3 30 (m, 4H), 3 48-3 52 (m, 4H), 3 78-3 90 (m, 4H), 4 80 (quintet, 1H), 7 29-7 35 (m, 2H), 7 61 (d, 2H), 7 99 (s, 1H), 8 75 (s, 1H), 10 04 (brs, 1H)	514
61	Tetrazol-1-yl CH_2-	1 42 (d, 6H), 2 78 (s, 3H), 3 20-3 28 (m, 2H), 3 32-3 40 (m, 2H), 3 70 3 85 (m, 4H), 4 80 (quintet, 1H), 5 72 (s, 2H), 7 20-7 26 (m, 2H), 7 59 (d, 2H), 7 99 (s, 1H), 8 74 (s, 1H), 9 31 (s, 1H), 10 04 (brs, 1H)	522
62	1*H*-Tetrazol-5-yl-CH_2-	(MeOD) 1 54 (d, 6H), 2 82 (s, 3H), 3 57-3 63 (m, 2H), 3 75-3 81 (m, 2H), 4 03-4 12 (m, 4H), 4 32 (s, 2H), 4 92 (quintet, 1H), 7 55 (d, 2H), 7 83 (d, 2H), 7 86 (s, 1H), 8 68 (s, 1H)	522
63	1-Methyl L-prolyl-	1 42 (d, 6H), 1 84-1 92 (m, 2H), 2 04-2 14 (m, 1H), 2 52-2 59 (m, 1H), 2 79-2 82 (m, 6H), 3 11-3 22 (m, 4H) 3 59-3 85 (m, 6H), 4 70-4 84 (m, 2H), 7 10 (d, 2H), 7 54 (d, 2H), 7 97 (s, 1H), 8 72 (s, 1H), 9 66 (brs, 1H), 9 93 (s, 1H)	523
64	$MeSO_2CH_2$-	1 42 (d, 6H), 2 79 (s, 3H), 3 11 (s, 3H), 3 22-3 30 (m, 4H), 3 78-3 88 (m, 4H), 4 54 (s, 2H), 4 80 (quintet, 1H), 7 23-7 27 (m, 2H), 7 59 (d, 2H), 7 98 (s, 1H), 8 74 (s, 1H), 10 02 (brs, 1H)	532

60

Examples 65-86

The following compounds were prepared by the procedure of Example 38 using the appropriate acid and 2-[4-(piperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine (Example 20)



Ex	R	H NMR (300MHz)	m/z
65	(R) HOCH(Me)	($CDCl_3$) 8 31 (d, 1H) 7 46 (d, 2H) 7 38 (s, 1H), 6 92 (d, 2H), 6 86 (d, 2H), 5 66 - 5 56 (m, 1H), 4 51 (q, 1H), 3 96 - 3 72 (m, 2H), 3 64 - 3 54 (m, 2H), 3 21 - 3 10 (m, 4H), 2 72 (brs, 1H), 2 62 (s, 3H), 1 48 (d, 6H), 1 37 (d, 3H)	450
66	Cyclopropyl	9 19 (s, 1H), 8 31 (d, 1H), 7 47 (d, 2H), 7 39 (s, 1H) 6 97 (s, 1H), 6 94 (d, 2H), 5 74 - 5 65 (m, 1H), 3 88 - 3 71 (m, 2H), 3 69 3 54 (m, 2H), 3 17 2 94 (m, 4H), 2 42 (s, 3H), 2 06 - 1 95 (m, 1H), 1 40 (d, 6H), 0 79 - 0 67 (m, 4H)	447
67	$MeOCH_2$-	9 18 (s, 1H), 8 33 (d, 1H), 7 49 (s, 1H), 7 47 (d, 2H), 6 96 (d, 1H), 6 92 (d, 2H), 5 72 - 5 63 (m, 1H), 4 13 (s, 2H), 3 62 - 3 49 (m, 4H), 3 29 (s, 3H), 3 11 - 3 00 (m, 4H), 2.48 (s, 3H), 1 40 (d, 6H)	450
68	(S)-MeOCH(Me)-	9 22 (s, 1H), 8 32 (d, 1H), 7 47 (d, 2H), 7 43 (s, 1H), 6 93 (d, 2H), 6 95 (s, 1H), 5 73 5 64 (m, 1H), 4.24 (q, 1H), 3 65 (d, 4H), 3 24 (s, 3H), 3 10 (brs, 4H), 2 47 (s, 3H), 1 40 (d, 6H), 1.23 (d, 3H)	464

Ex	R	H NMR (300MHz)	m/z
69	(S)-HOCH(Me)-	9 18 (s, 1H), 8 30 (s, 1H), 7 47 (d, 2H), 7 40 (s, 1H), 6 95 (d, 2H), 6 92 (d, 1H), 5 74 - 5 64 (m, 1H), 4 92 (d, 1H), 4 50 - 4 41 (m, 1H), 3 72 - 3 50 (m, 4H), 3 13 - 2 97 (m, 4H), 2 47 (s, 3H) 1 40 (d, 6H), 1.20 (d, 3H)	450
70	(R)-MeOCH(Me)	9.20 (s, 1H), 8 31 (d, 1H), 7 47 (d, 2H), 7 41 (s, 1H), 6 93 (d, 2H), 6 95 (s, 1H), 5 74 - 5 64 (m, 1H), 4.24 (q, 1H), 3 65 (d, 4H), 3 23 (s, 3H), 2 47 (s, 3H), 1 40 (d, 6H), 1 23 (d, 3H)	464
71	*i*-Pr-	9 21 (s, 1H) 8 31 (d, 1H), 7 47 (d, 2H), 7 40 (s, 1H), 6 94 (d, 1H), 6 92 (d, 2H), 5 74 - 5 64 (m, 1H), 3 67 (brs, 4H), 3 04 (d, 4H), 2 94 - 2 86 (m, 1H), 2 47 (s, 3H), 1 40 (d, 6H), 1 01 (d, 6H)	448
72	MeC(Me)(OH)CH_2-	9 19 (s, 1H), 8 30 (d, 1H) 7 47 (d, 2H) 7 38 (d, 1H), 6 94 (d, 1H), 6 92 (d, 2H) 5 74 - 5 64 (m, 1H), 4 80 (s, 2H), 3 68 - 3 59 (m, 4H) 3 29 (s, 1H), 3 10 - 2 98 (m, 4H), 2 47 (s, 3H), 1 39 (d, 6H), 1.20 (s, 6H)	478
73	2-(R)-Tetrahydrofur-2-yl	9 20 (s, 1H), 8 31 (d, 1H), 7 47 (d, 2H), 7 42 (s, 1H), 6 94 (d, 1H), 6 92 (d, 2H), 5 73 5 64 (m, 1H), 4 69 (t, 1H), 3 81 - 3 70 (m, 2H), 3 69 - 3 55 (m, 4H), 3 10 - 2 98 (m, 4H), 2 48 (s, 3H), 2 10 1 93 (m, 2H), 1 90 - 1 76 (m, 2H), 1 40 (d, 6H)	476
74	2-(S)-Tetrahydrofur-2-yl	9.20 (s, 1H), 8 32 (d, 1H), 7 47 (d, 2H), 7 42 (s, 1H), 6 94 (d, 1H), 6 92 (d 2H), 5 73 - 5 64 (m, 1H) 4 69 (t, 1H), 3 82 3 70 (m, 2H), 3 69 - 3 55 (m, 4H), 3 10 2 99 (m, 4H), 2 48 (s, 3H), 2 09 - 1 98 (m, 2H), 1 90 - 1 77 (m, 2H), 1 40 (d, 6H)	476

Ex	R	H NMR (300MHz)	m/z
75 [1]	1 Hydroxycycloprop-1 yl	9 95 (s, 1H), 8 62 (d, 1H), 8 22 (s, 1H), 7 76 - 7 57 (m, 4H), 7 18 (d, 1H), 5 64 - 5 55 (m, 1H), 4 24 - 3 87 (m, 4H), 3 51 (s, 4H), 2 82 (s, 3H) 1 50 (d, 7H), 1 04 - 0 97 (m, 2H) 0 83 0 77 (m, 2H)	462
76 [1]	(S)-MeCH$_2$CH(OH)-	9 83 (s, 1H), 8 60 (d, 1H), 8.20 (s, 1H), 7 65 (d, 2H) 7 50 (s, 2H), 7 15 (d, 1H), 5 64 - 5 54 (m, 2H), 4 97 (s, 1H), 4 25 (q, 1H), 3 99 - 3 70 (m, 4H), 3 42 - 3 25 (m, 4H), 2 81 (s, 3H), 1 72 - 1 58 (m, 2H), 1 49 (d, 6H), 0 89 (t, 3H)	464
77 [1]	(R)-MeCH$_2$CH(OH)-	9 90 (s, 1H), 8 61 (d, 1H) 8.21 (s, 1H), 7 68 (d, 2H), 7 50 (d, 2H), 7 16 (d, 1H), 5 64 - 5 55 (m, 1H), 4 25 (q, 1H), 4 02 - 3 73 (m, 4H), 3 45 - 3 30 (m, 4H), 2 80 (s, 3H), 1 72 1 57 (m, 2H), 1 49 (d, 6H), 0 89 (t, 3H)	464
78 [1]	1-Cyanocycloprop-1-yl	9 74 (s, 1H), 8 58 (d, 1H), 8 20 (s, 1H), 7 58 (d, 2H), 7 26 (d, 2H) 7 12 (d, 1H), 5 64 5 55 (m, 1H), 4 97 (brs, 1H), 4 00 - 3 76 (m, 4H), 3 36 3.25 (m, 4H), 2 80 (s, 3H), 1 65 - 1 53 (m, 4H), 1 48 (d, 6H)	471
79 [1]	(R)-MeCH(Me)CH(OH)-	9 98 (s, 1H), 8 62 (d, 1H), 8.23 (s, 1H), 7 71 (d, 2H), 7 58 (d, 2H), 7 18 (d, 1H), 5 64 - 5 55 (m, 1H), 5 38 (s, 2H), 4 07 (d, 1H), 4 04 - 3 78 (m, 4H), 3 48 3.35 (m, 4H), 2 82 (s, 3H), 1 94 1 82 (m, 1H), 1 50 (d, 6H), 0 87 (dd, 6H)	478
80 [1]	(S)-MeCH(Me)CH(OH)-	9 87 (s, 1H), 8 60 (d, 1H), 8.21 (s, 1H), 7 64 (d, 2H), 7 47 7 34 (m, 2H), 7 15 (d, 1H), 5 64 - 5 54 (m, 1H), 4 20 (brs, 2H), 4 08 (d, 1H), 3 98 - 3 70 (m, 4H), 3 38 - 3 25 (m, 4H), 2 81 (s, 3H), 1 93 - 1 82 (m, 1H), 1 49 (d, 6H), 0 88 (d, 3H), 0 85 (d, 3H)	478

Ex	R	H NMR (300MHz)	m/z
81 [1]	$MeOCH_2CH_2$-	10 04 (s, 1H), 8 62 (d, 1H), 8 24 (s, 1H), 7 20 (d, 1H), 5 66 - 5 56 (m, 1H), 4 80 (brs 1H) 4 02 (s, 4H), 3 58 (t, 2H), 3 52 (s, 4H), 3 26 (s, 3H), 2 84 (s, 3H), 2 65 (t, 2H), 1 50 (d, 6H)	464
82 [1]	$HOCH_2C(Me)_2$-	9 98 (s, 1H), 8 62 (d, 1H), 8 22 (s, 1H), 7 79 - 7 60 (m, 4H), 7 19 (d, 1H), 5 64 - 5 55 (m, 2H), 5 22 (s, 1H), 4 08 - 3 90 (m, 4H), 3 48 (s, 2H), 3 46 - 3 38 (m, 4H), 2 82 (s, 3H), 1 50 (d, 6H), 1 20 (s, 6H)	478
83 [1]	F_2CH-	9 73 (s, 1H), 8 57 (d, 1H), 8 20 (s, 1H), 7 57 (d, 2H), 7 22 (d, 2H), 7 12 (d, 1H), 6 79 (t, 1H), 5 64 5 55 (m, 1H), 4 69 (s, 1H), 3 83 - 3 71 (m, 4H), 3.34 - 3 21 (m, 4H), 2 80 (s, 3H), 1 47 (d, 6H)	456
84 [1]	$HC{\equiv}CCH_2OCH_2$-	9 89 (s, 1H), 8 60 (d, 1H), 8.23 (s, 1H), 7 67 (d, 2H), 7 55 - 7 41 (m, 2H), 7 16 (d, 1H), 5 64 - 5 55 (m, 1H), 4 60 (s, 1H), 4 29 (s, 2H), 4.24 (d, 2H), 3 49 (t, 1H), 2 81 (s, 3H), 1 50 (s, 6H)	474
85 [1]	$HOC(Me)_2$-	9 24 (brs, 1H), 8 55 (d, 1H), 7 54 (d, 2H), 7 19 – 7 13 (m, 2H), 7 09 (d, 1H), 5 63 – 5 54 (m, 1H), 4 84 (brs, 1H), 3 97 (s, 4H), 3 24 (s, 4H), 2 81 (s, 3H), 1 52 (d, 6H), 1 41 (s, 6H)	464
86 [1]	Et-	9 89 (s, 1H), 8 61 (d, 1H), 8 21 (s, 1H), 7 68 (d, 2H), 7 57 (s, 2H), 7 16 (d, 1H), 5 64 - 5 54 (m, 1H), 4 86 (s, 1H), 3 90 (s, 4H), 3 44 3 30 (m, 4H), 2 81 (s, 3H), 2 39 (q, 2H), 1 49 (d, 6H), 1 01 (t, 3H)	471

[1] The isolated free base was dissolved in EtOAc (3ml) with the addition of a few drops of MeOH to aid dissolution. 1 0M hydrogen chloride in ether solution (1 equivalent) was added, and the resultant hydrochloride salts were triturated with ether then filtered and dried *in vacuo*

Example 87

2-{4-[4-(Acetyl)piperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5 yl) 5-fluoropyrimidine

A solution of (2*Z*) 3-(dimethylamino)-2 fluoro-1-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one (Method 14,6 0g, 25mmol) and *N*-[4-(4-acetylpiperazin 1-yl)phenyl]guanidine bicarbonate salt (Method 2, 12 12g, 37 5mmol) in 2-methoxyethanol (90ml) was heated under reflux for 18hrs The reaction mixture was evaporated under reduced pressure and the title compound was isolated by MPLC on silica gel (3% MeOH / DCM) It was obtained as a crisp foam on evaporation. Yield = 8 9g (81%) NMR. 1 36 (d, 6H), 2 03 (s, 3H), [2 5 (s, 3H) under DMSO signal] 2 98 (m, 2H), 3 08 (m, 2H), 3 57 (m, 4H), 5 44 (septuplet, 1H), 6 90 (d, 2H), 7 34 (d, 1H), 7 42 (d, 2H), 8 44 (d, 1H), 9 24 (s, 1H), m/z 438

Example 88

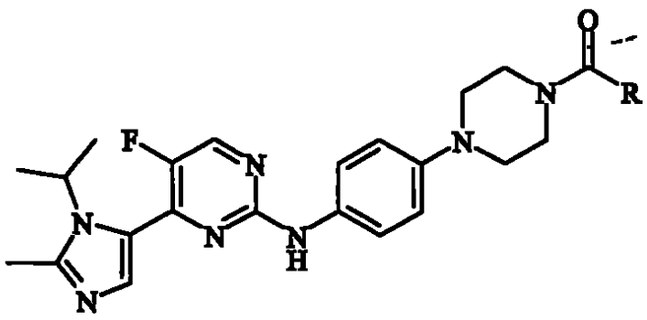
2-[4-(Piperazin-1 yl)anilino]-4-(1 isopropyl-2 methyl 1*H* imidazol-5-yl)-5-fluoropyrimidine hydrochloride

The title compound was prepared from 2-{4-[4-(acetyl)piperazin-1 yl]anilino}-4-(1-isopropyl-2-methyl 1*H*-imidazol-5-yl)-5-fluoropyrimidine (Example 87) by the procedure of Example 20) The title compound crystallized from the reaction mixture as the HCl salt and was filtered off, washed with isopropanol and ether Yield = 8 01g (98%) NMR 1 46 (d, 6H), 2 78 (s, 3H) 3 21 (brs, 4H), 3 32 (m, 4H), 5 24 (septuplet, 1H), 6 96 (d, 2H), 7 47 (d, 1H), 8 05 (d, 2H), 8 70 (d, 1H), 9 42 (brs, 1H), 9 65 (s, 1H), m/z 396

Examples 89-102

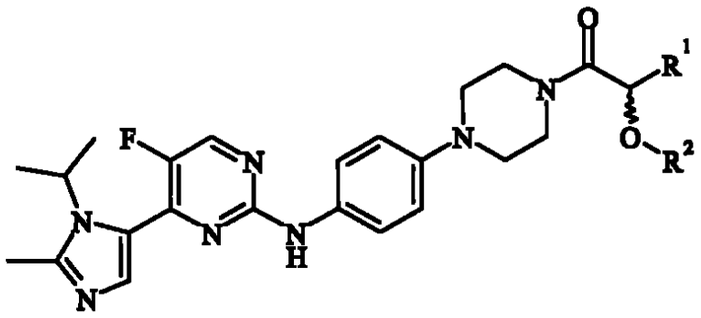
The following compounds were prepared by the procedure of Example 38 using the appropriate acid and 2-[4-(piperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine hydrochloride (Example 88)

For Examples 89-96, the isolated free bases were dissolved in EtOAc (3ml) with the addition of a few drops of MeOH to aid dissolution 1 0M hydrogen chloride in ether solution (1 equivalent) was added, and the resultant hydrochloride salts were triturated with ether then filtered and dried *in vacuo*



Ex	R	NMR ($CDCl_3$)	m/z
89	Et-	1 01 (t, 3H), 1 46 (d, 6H), 2 38 (q, 2H), 2 80 (s, 3H), 3 23-3 33 (m, 4H), 3 73-3 81 (m, 4H) 5 25 (quintet, 1H), 7 32 7 40 (m, 2H), 7 61 (d, 2H), 8 07 (d, 1H), 8 75 (d, 1H) 9 85 (brs, 1H)	452
90	$HOCH_2CH_2$-	1 46 (d, 6H), 2 53 (t, 2H), 2 78 (s, 3H), 3 10-3 17 (m, 4H), 3 62-3 68 (m, 4H), 3 70 (t, 2H), 5 28 (quintet, 1H), 6 97 (d, 2H), 7 44 (d, 2H), 7 90 (d, 1H), 8 60 (d, 1H) 9 18 (brs, 1H)	468
91	$MeOCH_2CH_2$-	1 45 (d, 6H), 2 62 (t, 2H), 2 79 (s, 3H), 3 14-3 22 (m, 4H), 3 23 (s, 3H), 3 57 (t, 2H), 33 69-3 77 (m, 4H), 5 25 (quintet, 1H), 7 18-2 26 (m, 2H), 7 55 (d, 2H), 8 06 (d, 1H), 8 73 (d, 1H), 9 76 (brs, 1H)	482
92	$MeOCH_2$-	1 47 (d, 6H), 2 80 (s, 3H), 3 30 (s, 3H), 3 31-3 38 (m, 4H), 3 73-3 82 (m, 4H), 4 15 (s, 2H), 5 24 (quintet, 1H), 7 40-7 47 (m, 2H), 7 63 (d, 2H), 8 08 (d, 1H), 8 76 (d, 1H), 9 90 (brs, 1H)	468
93	*i*-Pr-	1 01 (d, 6H), 1 45 (d, 6H), 2 75 (s, 3H), 2 90 (quintet, 1H), 3 10-3 18 (m, 4H) 3 66-3 74 (m, 4H), 5 25 (quintet, 1H), 7 08-7 16 (m, 2H), 7 51 (d, 2H), 8 06 (d, 1H), 8 72 (d, 1H), 9 69 (brs, 1H)	466
94	(*R*)-MeCH(OH)-	1 10 (d, 3H), 1 45 (d, 6H), 2 79 (s, 3H), 3 20-3 33 (m, 4H), 3 75-3 87 (m, 4H), 4 47 (q, 1H) 5.25 (quintet, 1H), 7.27-7 33 (m, 2H), 7 57 (d, 2H), 8 07 (d, 1H), 8 73 (d, 1H) 9 81 (brs, 1H)	468

Ex	R	NMR ($CDCl_3$)	m/z
95	MeC(Me)(OH)-	1 34 (s, 36H), 1 47 (d, 6H), 2 80 (s, 3H), 3 34-3 41 (m, 4H), 3 80-4 00 (m, 4H) 5 24 (quintet, 1H), 7 47-7 55 (m, 2H), 7 65 (d, 2H), 8 08 (d, 1H), 8 77 (d, 1H), 9 92 (brs, 1H)	482
96	(*S*)-MeCH(OH)-	1 21 (d, 3H), 1 48 (d, 6H), 2 78 (s, 3H), 3 15 (b s, 4H), 3 74 (b s, 4H), 4 46 (q, 1H), 5 27 (septuplet, 1H), 7 90 (b s, 2H), 7 50 (b d, 2H) 8 09 (d, 1H), 8 72 (d, 1H), 9 57 (b s, 1H)	468



Ex	R^1	R^2	*form*	NMR ($CDCl_3$)	^{19}F NMR	m/z
97	Et	H	R	1 02 (t, 3H), 1 47 (d, 6H), 1 55 (m, 1H), 1 75 (m, 1H), 2 59 (s, 3H), 3 15 (m, 4H), 3 58 (brs, 2H), 3 69 (d, 1H), 3 80 (m, 1H), 3 88 (m, 1H), 4 36 (m, 1H), 5 54 (septuplet, 1H), 6 80 (s, 1H), 6 92 (d, 2H), 7 40 (d, 2H), 7 57 (d, 1H), 8 23 (d, 1H)	-147 82	482
98	Me	Me	*R*	1 42 (d, 3H), 1.47 (d, 6H), 2 59 (s, 3H), 3 15 (m, 4H), 3 38 (s, 3H) 3 80 (m, 4H), 4 20 (q, 1H), 5 54 (septuplet, 1H), 6 80 (s, 1H), 6 92 (d, 2H), 7 40 (d, 2H), 7 57 (d, 1H), 8.23 (d, 1H)	-147 93	482

Ex	R^1	R^2	*form*	NMR ($CDCl_3$)	^{19}F NMR	m/z
99 [1]	i-*Pr*	H	*R*	0 83 (d, 3H), 1 10 (d, 3H), 1 47 (d, 6H), 1 55 (m, 1H), 1 87 (septuplet, 1H), 2 59 (s, 3H), 3 13 (m, 4H) 3 58 (m, 3H) 3 69 (d, 1H), 3 80 (m, 1H), 3 88 (m, 1H), 4 28 (dd, 1H), 5 54 (septuplet, 1H), 6 80 (s, 1H), 6 91 (d, 2H), 7 40 (d, 2H), 7 57 (d, 1H), 8 23 (d, 1H)	-147 82	496
100	Et	H	*S*	1 02 (t, 3H), 1 47 (d, 6H), 1 55 (m, 1H), 1 75 (m, 1H), 2 59 (s, 3H), 3 15 (m, 4H), 3 58 (brs, 2H), 3 69 (d, 1H), 3 80 (m, 1H), 3 88 (m, 1H), 4 36 (m, 1H), 5 54 (septuplet, 1H), 6 80 (s, 1H), 6 92 (d, 2H), 7 40 (d, 2H), 7 57 (d, 1H), 8 23 (d, 1H)	-147 82	482
101	Me	Me	*S*	1 42 (d, 3H), 1 47 (d, 6H), 2 59 (s, 3H), 3 15 (m, 4H), 3 38 (s, 3H), 3 80 (m, 4H), 4 20 (q, 1H), 5 54 (septuplet, 1H), 6 80 (s, 1H), 6 92 (d, 2H), 7 40 (d, 2H), 7 57 (d, 1H), 8 23 (d, 1H)	-147 93	482
102 [2]	i-*Pr*	H	*S*	0 83 (d, 3H), 1 10 (d, 3H), 1 47 (d, 6H), 1 55 (m, 1H), 1 87 (septuplet, 1H), 2 59 (s, 3H), 3 13 (m, 4H) 3 58 (m, 3H), 3 69 (d, 1H), 3 80 (m, 1H), 3 88 (m, 1H), 4 28 (dd, 1H), 5 54 (septuplet, 1H), 6 80 (s, 1H), 6 91 (d, 2H), 7 40 (d, 2H), 7 57 (d, 1H), 8 23 (d, 1H)	-147 82	496

[1] Chromatography with 5% MeOH.NH_3 (7N) in DCM EtOAc (1 1) solution

[2] Compound required further chromatography eluting with 5% MeOH in EtOAc

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Example 103

2-{4-[4-(2-Acetoxyacetyl)piperazin-1-yl]anilino}-4-(1 isopropyl-2-methyl-1*H*-imidazol 5-yl)-5-fluoropyrimidine

The title compounds was prepared using the procedure of Example 21 using 2-[4-(piperazin-1-yl)anilino]-4-(1-isopropyl 2-methyl-1*H*-imidazol-5 yl)-5 fluoropyrimidine hydrochloride (Example 88, 200mg 0 5 mmol) After work-up, the mixture was purified by chromatography on silica gel using MeOH DCM (3 97 to 6 94) to give a solid 170 mg M/z 496

Example 104

2-{4-[4-(2-Hydroxyacetyl)piperazin-1 yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)-5 fluoropyrimidine hydrochloride

2-{4-[4-(2-Acetoxyacetyl)piperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine (Example 103) was deprotected by the procedure of Example 22 The reaction mixture was evaporated under reduced pressure The residue was dissolved in DCM (15 ml), washed with water(10ml) and brine (10ml), dried and evaporated. The residue was triturated with ether and re-evaporated to give the title compound as a solid 134 mg. This was converted to the hydrochloride salt from EtOH by the addition of 1M ether / HCl. After evaporation and trituration with ether a solid was obtained. NMR. 1 46 (d, 6H), 2 78 (s, 3H), 3 14 (b s, 4H), 3 58 (b s, 2H), 3 68 (b s, 2H), 4 13 (s, 2H), 5 26 (septuplet, 1H), 7 10 (b s, 2H), 7 50 (d, 2H), 8 08 (d, 1H), 8 72 (d, 1H), 9 68 (b s, 1H), m/z 454

Example 105

2-{4-[4-(Acetyl)piperazin-1 yl]anilino}-4-(1-cyclobutyl-2 methyl-1*H*-imidazol-5-yl)-5 fluoropyrimidine

The title compound was prepared from (2*Z*)-1-(1-cyclobutyl-2-methyl-1*H*-imidazol 5-yl)-3-(dimethylamino)-2 fluoroprop-2-en-1-one (Method 16, 1 406g) and *N* [4-(4-acetylpiperazin-1-yl)phenyl]guanidine bicarbonate salt (Method 2, 2 71g) by the procedure of Example 18 to yield a white solid (2.21g, 88%) NMR. 1 61-1 72 (m, 2H), 2 06 (s, 3H), 2 30-2 43 (m, 4H), 2 75 (s, 3H) 3 27 3 39 (m, 4H), 3 77-3 85 (m, 4H), 5 22 (quintet, 1H), 7 42-7 48 (m, 2H), 7 69 (d, 2H), 8 09 (d, 1H), 8 74 (d, 1H), 9 97 (brs 1H), m/z 450

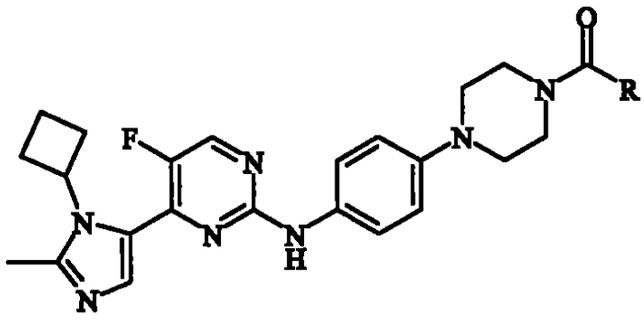
Example 106

2-[4-(Piperazin-1-yl)anilino]-4-(1-cyclobutyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine

The title compound was prepared from 2-{4-[4-(acetyl)piperazin-1-yl]anilino}-4-(1-cyclobutyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine (Example 105, 1.89g) by the procedure of Example 20 to yield a yellow solid (1.538g, 90%). NMR ($CDCl_3$) 1.61-1.78 (m, 2H), 2.35-2.45 (m, 4H), 2.59 (s, 3H), 3.03-3.09 (m, 4H), 3.10-3.15 (m, 4H), 5.33 (quintet, 1H), 6.93 (s, 1H), 6.95 (d, 2H), 7.42 (d, 2H), 7.49 (d, 1H), 8.22 (d, 1H), m/z 408

Examples 107-110

The following compounds were prepared by the procedure of Example 38 using the appropriate acid and 2-[4-(piperazin-1-yl)anilino]-4-(1-cyclobutyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine (Example 106). The isolated free bases were dissolved in EtOAc (3ml) with the addition of a few drops of MeOH to aid dissolution. 1.0M hydrogen chloride in ether solution (1 equivalent) was added, and the resultant hydrochloride salts were triturated with ether then filtered and dried *in vacuo*



Ex	R	NMR (300MHz, $CDCl_3$)	m/z
107	$HOCH_2$-	1.61-1.72 (m, 2H), 2.31-2.44 (m, 4H), 2.75 (s, 3H), 3.28-3.36 (m, 4H), 3.70-3.85 (m, 4H), 4.15 (s, 2H), 5.22 (quintet, 1H), 7.42 (m, 2H, 7.68 (d, 2H), 8.09 (s, 1H), 8.74 (1H, s), 9.95 (brs, 1H)	466
108	(*S*)-MeCH(OH)-	1.22 (d, 3H), 1.63-1.72 (m, 2H), 2.30-2.43 (m, 4H), 2.75 (s, 3H), 3.30-3.38 (m, 4H), 3.80-3.96 (m, 4H), 4.46 (q, 1H), 5.22 (quintet, 1H), 7.39-7.47 (m, 2H), 7.68 (d, 2H), 8.08 (d, 1H), 8.74 (d, 1H), 9.95 (brs, 1H)	480

Ex	R	NMR (300MHz, $CDCl_3$)	m/z
109	(*R*)-MeCH(OH)-	1 22 (d, 3H), 1 63-1 72 (m, 2H), 2 30 2 43 (m, 4H), 2 75 (s, 3H), 3 30-3 38 (m, 4H), 3 80-3 96 (m, 4H), 4 46 (q, 1H), 5.22 (quintet, 1H) 7 39-7 47 (m, 2H), 7 68 (d 2H) 8 08 (d, 1H), 8 74 (d, 1H), 9 95 (brs, 1H)	480
110	$MeOCH_2$-	1 62-1 72 (m, 2H) 2 30-2 44 (m, 4H), 2 75 (s, 3H), 3 31 (s, 3H), 3 32 3 39 (m, 4H), 3 75 3 85 (m, 4H), 4 16 (s, 2H), 5 22 (quintet, 1H), 7 43-7 50 (m, 2H), 7 70 (d, 2H), 8 09 (d, 1H), 8 75 (d, 1H), 9 99 (brs, 1H)	480

Example 111

2-[4-(Morpholino)anilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine

(2*E*)-3-(Dimethylamino) 1-(1 isopropyl-2-methyl 1*H*-imidazol-5-yl)prop-2-en-1-one (Method 24 of WO 03/076436), (110mg 0 5mmol) and *N*-[4-(morpholino)phenyl]guanidine bicarbonate salt (Method 4, 170mg 0 6mmol) in dimethylacetamide (4ml) were heated for 20 minutes at 200°C in a microwave The reaction mixture was evaporated under reduced pressure and the residue purified by chromatography on silica gel with MeOH DCM (4 96 to 8 92) to give the title compound, after trituration with ether, as a solid 90mg 50% NMR 1 42 (d, 6H), 2 48 (s, 3H), 3 06 (t, 4H), 3 75 (t, 4H), 5 71 (septuplet, 1H), 6 91 (d, 2H), 6 97 (d, 1H), 7 40 (s, 1H), 7 48 (d, 2H) 8 32 (s, 1H), 9 18 (s, 1H), m/z 379

Example 112

2-[4-(Morpholino)anilino]-4-(1-ethyl-2-methyl-1*H*-imidazol-5 yl)-5-fluoropyrimidine hydrochloride

(2*E*)-3-(Dimethylamino)-1-(1-ethyl-2-methyl-1*H*-imidazol 5 yl) 2 fluoro-prop-2-en-1-one (Method 15, 250mg 1 11mmol) and *N*-[4-(morpholino)phenyl]guanidine bicarbonate salt (Method 4, 405mg 1 44mmol) in 2 methoxyethanol (4 5ml) were heated for 30 minutes at 200°C in a microwave The reaction mixture was evaporated under reduced pressure and the residue purified by chromatography on neutral alumina (activityII) with MeOH DCM EtOAc (1 79 5 19 5) to give the title compound, after trituration with ether, as a solid 230mg 54% This was converted to the hydrochloride salt from MeOH with 1M ether/HCl. Trituration with ether and evaporation gave the title compound as a solid. NMR 1 19 (t, 3H),

2 70 (s, 3H), 3 12 (b s, 4H), 3 60 (b s, exchangeables), 3 79 (t, 4H), 4 59 (q, 2H), 7 05 (b s, 2H), 7 44 (d, 2H), 8 20 (d, 1H), 8 68 (d, 1H), 9 54 (s, 1H), m/z 383

Example 113

2-[4-(Morpholino)anilino]-4-(1-isopropyl-2 methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine

(2*E*)-3 (Dimethylamino)-2-fluoro-1 (1-isopropyl-2-methyl-1*H* imidazol-5-yl)prop-2-en-1-one (Method 14, 240mg 1 0mmol) and *N*-[4-(morpholino)phenyl]guanidine bicarbonate salt (Method 4, 367mg 1 3mmol) in 2 methoxyethanol (4 5ml) were heated for 40 minutes at 160°C then 20 minutes at 180°C in a microwave. The reaction mixture was evaporated under reduced pressure and the residue purified by chromatography on silica gel with MeOH.DCM EtOAc (4 48 48 to 10 45 45) to give the title compound as a solid 180mg 45% This was converted to the hydrochloride salt from MeOH with 1M ether/HCl. Trituration with ether and evaporation gave the title compound as a solid. NMR (373K) 1 48 (d, 6H), 2 77 (s, 3H), 3 09 (t, 4H), 3 78 (t, 4H) 5 30 (septuplet, 1H), 6 94 (d, 2H), 7 43 (d, 2H), 7 88 (d, 1H), 8 602 (d, 1H), m/z 397

Example 114

2-[4-(Morpholino)anilino]-4-(1-cyclobutyl 2-methyl-1*H*-imidazol-5-yl)pyrimidine

The title compound was prepared from (2*E*)-1-(1-cyclobutyl 2-methyl-1*H*-imidazol-5-yl)-3-(dimethylamino)prop-2-en-1-one (Method 37 of WO 03/076435, 233mg) and *N*-(4-morpholin-4-ylphenyl)guanidine (Method 4, 405mg) by the procedure of Example 111 to yield a white solid (228mg, 61%) NMR. 1 59-1 72 (m, 2H), 2 32-2 44 (m, 4H), 2 75 (s, 3H), 3 21-3 28 (m, 4H), 3 84-3 92 (m, 4H), 5 40 (quintet, 1H), 7 09 (d, 1H), 7 24-7 32 (m, 2H), 7 66 (d, 2H), 8 11 (s, 1H), 8 57 (d, 1H), 9 77 (brs, 1H), m/z 391

Example 115

2-[4-(Morpholino)anilino]-4-(1-cyclobutyl 2 methyl 1*H*-imidazol-5-yl)-5-fluoropyrimidine

The title compound was prepared from (2*Z*)-1-(1-cyclobutyl-2-methyl-1*H*-imidazol-5-yl)-3-(dimethylamino)-2-fluoroprop-2-en 1-one (Method 16, 234mg) and *N*-(4-morpholin-4-ylphenyl)guanidine (Method 4, 410mg) by the procedure of Example 111 to yield a white solid (288mg, 76%) NMR 1 61-1 72 (m, 2H), 2.29-2 45 (m, 4H), 2 75 (s, 3H), 3.26-3 34 (m, 4H), 3 90-3 97 (m, 4H), 5.22 (quintet, 1H), 7 38-7.45 (m, 2H), 7 68 (d, 2H), 8 08 (d, 1H), 8 73 (d, 1H), 9 95 (brs, 1H), m/z 409

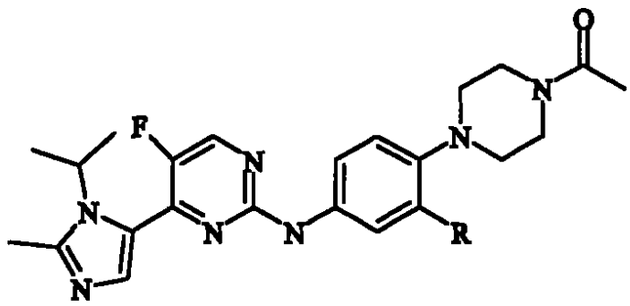
Example 116

2-{4-[4-(Acetyl)piperazin-1-yl]3 methylanilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine

A solution of (2*Z*)-3-(dimethylamino)-2-fluoro-1-(1-isopropyl-2 methyl 1*H*-imidazol-5 yl)prop-2-en-1-one (Method 14, 1 53g, 6 4mmol) and *N*-[4-(4-acetylpiperazin-1-yl)3-methylphenyl] guanidine bicarbonate salt (Method 31, 3 23g, 9 60mmol) in 2-methoxyethanol (10ml) was heated under reflux for 24hrs The reaction mixture was evaporated under reduced pressure and the residue purified by chromatography on silica gel with MeOH DCM EtOAc (1 49 5 49 5 to 10 45 45) to give a solid which required further purification with MeOH DCM (1 99 to 10 90) After trituration with ether and evaporation of the solvent, the title compound was obtained as a crisp foam which was dried in vac oven overnight at 50°C (1 91g, 66%) NMR (400MHz) 1 40 (d, 6H), 2 05 (s, 3H), 2 26 (s, 3H), 2 55 (s, 3H, under DMSO signal), 2 77 (dt, 4H), 3 58 (m, 4H), 5 41 (septet, 1H), 6 98 (d, 1H), 7 34 (d, 1H), 7 35 (d, 1H), 7 42 (dd, 1H), 8 49 (d, 1H), 9 28 (s, 1H), ^{19}F NMR (400MHz) -149 40 (t, 1F), m/z 452

Example 117-118

The following compounds were prepared using the procedure of Example 116 from (2*Z*)-3-(dimethylamino)-2-fluoro-1-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en 1-one (Method 14) and the appropriate guanidine



Ex	R	NMR (400MHz)	m/z	SM
117 1	Cl	1 43 (d, 6H), 2 05 (s, 3H), 2 51 (s, 3H, under DMSO signal), 2 89 (dt, 4H), 3 59 (m, 4H), 5 37 (septet, 1H) 7 12 (d, 1H), 7 36 (d, 1H), 7 53 (dd, 1H), 7 77 (d, 1H), 8 55 (d, 1H), 9 54 (s, 1H), ^{19}F NMR (400MHz) -148 33 (t, 1F)	472-474	Method 32

Ex	R	NMR (400MHz)	m/z	SM
118 [2]	F	1 44 (d, 6H), 2 04 (s, 3H), 2 57 (s, 3H, under DMSO signal), 2 92 (dt, 4H), 3 58 (m, 4H), 5 42 (septet, 1H), 7 00 (t, 1H), 7 30 (dd, 1H), 7 36 (d, 1H), 7 58 (dd, 1H), 8 55 (d, 1H) 9 55 (s, 1H), ^{19}F NMR (400 MHz) 148 47 (t, 1F)	456	Method 33

[1] Chromatography with MeOH DCM EtOAc(1 49 5 49 5 to 10 45 45) (469 8 mg, 69%)

[2] Chromatography with MeOH DCM.EtOAc (1 49 5 49 5 to 10 45 45) (2 72g, 72%)

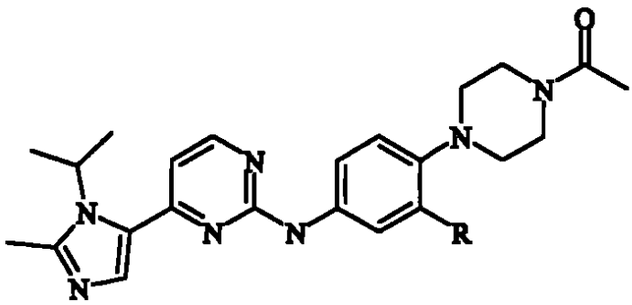
Example 119

2-{4-[4-(Acetyl)piperazin-1-yl]3-methylanilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl) pyrimidine

The title compound was prepared from (2*E*)-3-(dimethylamino)-1-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one (Method 24 of WO 03/076436, 331 8g, 1 5mmol) and *N*-[4-(4-acetylpiperazin-1-yl)3-methylphenyl]guanidine bicarbonate salt (Method 31, 758 3mg, 2 25mmol) by the procedure of Example 116 The reaction mixture was evaporated under reduced pressure and the residue purified by chromatography on silica gel with MeOH DCM EtOAc (1 49 5 49 5 to 10 45 45) to give a solid (419 4mg, 65%) NMR. 1 41 (d, 6H), 2 05 (s, 3H), 2 27 (s, 3H), 2 48 (s, 3H), 2 77 (dt, 4H), 3 58 (m, 4H), 5 66 (septet, 1H), 6 97 (d, 1H), 6 99 (d, 1H), 7 37 (d, 1H), 7 41 (s, 1H), 7 47 (dd, 1H), 8 35 (d, 1H), 9 20 (s, 1H), m/z 434

Examples 120-121

The following compounds were prepared using the procedure of Example 119 from (2*E*)-3-(dimethylamino)-1-(1 isopropyl-2-methyl-1*H* imidazol 5 yl)prop-2-en-1-one (Method 24 of WO 03/076436) and the appropriate guanidine.



Ex	R	NMR (400MHz)	m/z	SM
120[1]	Cl	1 45 (d, 6H), 2 05 (s, 3H), 2 50 (s, 3H+DMSO), 2 90 (dt, 4H), 3 59 (m, 4H), 5 62 (septet, 1H), 7 05 (d, 1H), 7 12 (d, 1H), 7 43 (s, 1H), 7 57 (dd, 1H), 7 81 (d, 1H), 8 40 (d, 1H), 9 45 (s, 1H)	454-456	Method 32
121[2]	F	1 45 (d, 6H), 2 04 (s, 3H), 2 57 (s, 3H+DMSO), 2 93 (dt, 4H), 3 59 (m, 4H), 5 68 (septet, 1H), 7 00 (t, 2H), 7 05 (d, 2H), 7 33 (dd, 1H), 7 42 (s, 1H), 7 64 (dd, 1H), 8 39 (d, 1H), 9 46 (s, 1H)	438	Method 33

[1] This compound required further chromatography on Basic prep HPLC with acetonitrile 1% NH_3 / H_2O (25 75 to 70 30) (475 mg, 52%)

[2] (413 5mg, 63%)

Example 122

2-[4-(Piperazin-1-yl)3-methylanilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol-5 yl) 5-fluoropyrimidine

2-{4-[4-(Acetyl)piperazin-1 yl]3-methylanilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol 5-yl)-5 fluoropyrimidine (Example 116, 1 89g, 4 19mmol) was stirred and heated in isopropanol (20ml), H_2O (5ml) and 33% hydrochloric acid (4ml) at 90°C for 10 hours The solvent was evaporated under reduced pressure to give a residue which was partitioned between water and DCM, basified with sat. sodium hydrogen carbonate and the aqueous layer was extracted with DCM twice The organics were combined, washed with brine, dried and evaporation of solvent to give the title compound as a crisp foam which was dried in vac oven overnight at 50°C (1 53g, 89%) NMR (400 MHz) 1 39 (d, 6H), 2 23 (s, 3H), 2 51 (s, 3H, under DMSO signal), 2 72 (m, 4H), 2 85 (m, 4H), 3 29 (s, 1H under H_2O signal), 5 42 (septet, 1H), 6 95 (d, 1H), 7 30 (d, 1H), 7 35 (d, 1H), 7 40 (dd, 1H), 8 48 (d, 1H), 9 24 (s, 1H), ^{19}F NMR (400MHz) 149 59 (t, 1F), m/z 410

Example 123

2-[4-(Piperazin 1-yl)3 fluoroanilino]-4-(1-isopropyl-2-methyl 1*H*-imidazol-5-yl)-5-fluoropyrimidine

The compound was prepared from 2-{4-[4-(acetyl)piperazin-1-yl]3-fluoroanilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine (Example 118, 455mg, 1mmol) by the procedure of Example 122 The title compound was obtained as a crisp foam which was dried in vac oven overnight at 50°C (337 8mg, 82%) NMR (400 MHz) 1 41 (d, 6H), 2 23

(s, 3H), 2 50 (s, 3H, under DMSO signal), 2 90 (s, 8H), 3 29 (s, 1H under H_2O signal), 5 43 (septet, 1H), 6 96 (t, 1H) 7 29 (dd, 1H), 7 36 (d, 1H), 7 53 (dd, 1H), 8 53 (d, 1H), 9 50 (s, 1H), ^{19}F NMR (400MHz) -148 60 (t, 1F), m/z 414

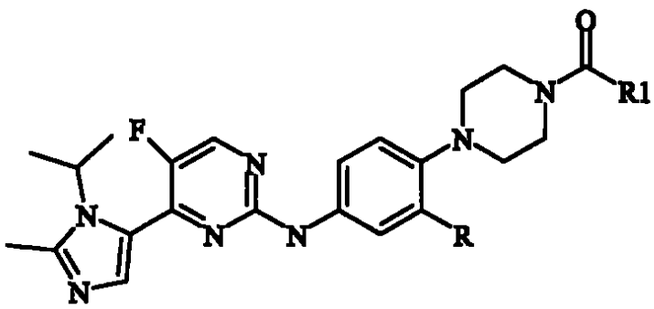
Example 124

2-{4-[4-((2S)-2-Hydroxypropionyl)piperazin-1-yl]3-methylanilino}-4-(1 isopropyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine

A solution of 2-[4-(piperazin 1-yl)3-methylanilino]-4-(1-isopropyl-2 methyl-1*H*-imidazol-5-yl)-5 fluoropyrimidine (Example 122, 490 8mg, 1 20mmol), L-lactic acid (129 7mg, 1 44mmol), HOBt.H_2O (220 5mg, 1 44mmol) and DIPEA (0 24ml, 1 44mmol) in DMF (5ml) was cooled to 0°C, followed by addition of EDAC (230 05mg, 1 44mmol) in portions. The mixture was then stirred at ambient temperature for 3 5 hours The solution was concentrated *in vacuo* then the residue was partitioned between DCM and water + sat. sodium hydrogen carbonate The organic extract was washed with water (3 times), brine, dried and concentrated. To a solution of crude product in MeOH (5ml) was added 1 pellet of KOH and the mixture was stirred at ambient temperature for 20min. The residue obtained on evaporation was purified by chromatography on silica gel with MeOH DCM (1 99 to 5 95) to yield the title compound, after trituration with ether, as a solid which was dried in vac oven overnight at 50°C (415mg, 72%) NMR. (500 MHz at 373K) 1 27 (d, 3H), 1 40 (d, 6H), 2 28 (s, 3H), 2 48 (s, 3H, under DMSO signal), 2 82 (m, 4H), 3 65 (m, 4H), 4 47 (m, 2H), 5 38 (septet, 1H), 7 00 (d, 1H), 7 35 (m, 2H), 7 40 (dd, 1H), 8 40 (d, 1H), 8 80 (s, 1H), ^{19}F NMR (400MHz) -149.33 (t, 1F), m/z 482

Examples 125-128

The following compounds were prepared by the procedure of Example 124 using the appropriate acid and pyrimidine.



Ex	R	R1	NMR (500MHz) at 373K	m/z	SM
125[1]	Me	CH_2OH	1 40 (d, 6H), 2 27 (s, 3H), 2 50 (s, 3H, under DMSO signal), 2 80 (m, 4H), 3 57 (m, 4H), 4 13 (d, 2H), 4 20 (t, 1H), 5 37 (septet, 1H), 6 98 (d, 1H), 7 31 (m, 2H) 7 38 (dd, 1H), 8 40 (d, 1H), 8 80 (s, 1H), ^{19}F NMR (400MHz) -149 31 (t, 1F)	468	Example 122
126[2]	F	CH_2OH	1 44 (d, 6H), 2 59 (s, 3H under DMSO signal), 2 94 (brs, 4H), 3 57 (brd, 4H), 4 13 (brd, 2H), 4 59 (br t, 1H), 5 43 (septet, 1H), 7 00 (t, 1H), 7 30 (dd, 1H), 7 36 (d, 1H), 7 58 (dd, 1H), 8 55 (d, 1H), 9 55 (s, 1H), ^{19}F NMR -148 46 (t, 1F)	472	Example 123
127[3]	F	*(S)*-MeCH(OH)-	1 25 (d, 3H), 1 44 (d, 6H), 2 50 (s, 3H, under DMSO signal), 3 00 (m, 4H), 3 66 (m, 4H), 4 46 (m, 2H), 5 38 (septet, 1H), 6 99 (t, 1H), 7 28 (dd, 1H), 7 33 (d, 1H), 7 49 (dd, 1H), 8 44 (d, 1H), 9 09 (s, 1H), ^{19}F NMR (500MHz) 148 40 (t, 1F), -122 6 (s, 1F)	486	Example 123
128[4]	F	CH_2OMe	1 43 (d, 6H), 2 50 (s, 3H, under DMSO signal), 3 00 (m, 4H), 3 33 (s, 3H), 3 60 (m, 4H), 4 10 (s, 2H), 5 40 (septet, 1H), 7 00 (t, 1H), 7 30 (dd, 1H), 7 33 (d, 1H), 7 50 (dd, 1H), 8 43 (d, 1H), 9 09 (s, 1H), ^{19}F NMR (500MHz) 148 40 (t, 1F), -122 7 (s, 1F)	486	Example 123

[1] Extra acid (9mg) and EDAC (23mg) added and Reaction time = 4 5h, (365mg, 65%)

[2] Extra acid (10mg) and EDAC (20mg) added and Reaction time = 5 5h, NMR (400MHz, RT) Chromatography with MeOH.DCM (1 99 to 6 94), (334 5mg, 71%)

[3] Extra acid (10mg) and EDAC (19mg) added and Reaction time = 6h, (378mg, 78%)

[4] No need to treat the crude product with KOH in MeOH, (310mg, 64%)

Example 129

2-{4-[(3*R*,5*S*)-4-Acetyl-3,5-dimethylpiperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine

The title compound was prepared from (2*Z*)-3-(dimethylamino)-2-fluoro-1-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one (Method 14, 331mg, 1.38mmol) and *N*-[4-((3*R*,5*S*)-4-acetyl-3,5-dimethylpiperazin-1-yl)phenyl]guanidine (Method 34, 737.1mg, 2.10mmol) by the procedure of Example 116. The reaction mixture was evaporated under reduced pressure and the residue purified by chromatography on silica gel with MeOH:DCM:EtOAc (1:49:5 49:5 to 10:45:45) to give a solid which was dried in vac oven overnight at 50°C (485mg, 76%) NMR. (400MHz) 1.30 (s, 6H), 1.41 (d, 6H), 2.05 (s, 3H), 2.50 (s, 3H under DMSO signal), 2.73 (m, 2H), 3.40 (d, 2H), 4.30 (brs, 2H), 5.45 (septet, 1H), 6.95 (d, 2H), 7.35 (d, 1H), 7.45 (d, 2H), 8.49 (d, 1H), 9.25 (s, 1H), ^{19}F NMR (400 MHz) -149.80 (t, 1F), m/z 466

Example 130

2-{4-[(2*S*,5*R*)-4-Acetyl-2,5-dimethylpiperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine

The title compound was prepared from (2*Z*)-3-(dimethylamino)-2-fluoro-1-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one (Method 14, 335mg, 1.40mmol) and *N*-[4-((2*S*,5*R*)-4-acetyl-2,5-dimethylpiperazin-1-yl)phenyl]guanidine (Method 35, 737.1mg, 2.10mmol) by the procedure of Example 116. The reaction mixture was evaporated under reduced pressure and the residue purified by chromatography on silica gel with MeOH:DCM:EtOAc (1:49:5 49:5 to 6:47:47) to give a solid which required further purification with MeOH:DCM (1:99 to 6:94). After trituration with ether and evaporation of the solvent, the title compound was obtained as a solid which was dried in vac oven overnight at 50°C (330mg, 51%). NMR. (500 MHz) 0.95 (d, 3H), 1.33 (d, 3H), 1.40 (d, 6H), 2.03 (s, 3H), 2.50 (s, 3H+DMSO), 3.17 (m, 2H), 3.43 (brs, 1H), 3.83 (brs, 1H), 4.00 (m, 1H), 4.47 (brs, 1H), 5.40 (septet, 1H), 6.83 (d, 2H), 7.32 (d, 1H), 7.37 (d, 2H), 8.35 (d, 1H), 8.7 (s, 1H), ^{19}F NMR (500 MHz MHz) -149.95 (t, 1F), m/z 466

Example 131

2-(3-Chloro-4-piperazin 1-yl)anilino-4-(1 isopropyl-2 methyl-1*H*-imidazol-5 yl)pyrimidine hydrochloride

2-[3-Chloro-4-(4-acetylpiperazin-1 yl)anilino]-4-(1-isopropyl-2-methyl-1*H* imidazol-5-yl)pyrimidine (Example 120, 4 1g, 9 1mmol) was stirred and heated in isopropanol (41ml) and 33% hydrochloric acid (4 1ml) at 85°C for 25 hours The reaction was evaporated under reduced pressure and then diluted with water (200ml), washed with DCM (200ml), basified with aqueous saturated sodium bicarbonate solution and extracted with chloroform (2 x 400ml) The solution was dried and evaporated under reduced pressure to give the amine, which was converted to the hydrochloride salt by dissolving in MeOH DCM (60ml, 1 1) and treating with a 1 0 molar solution of ethereal HCl (9 1ml) The solid was triturated with ether (40ml) and filtered to give the title compound (3 2g, 77%) NMR 1 42 (d, 6H), 2 61 (s, 3H) 3 16 (m, 4H), 3.40 (m, 4H), 5 58 (septet, 1H), 7 10 (d, 1H), 7 14 (d, 1H), 7 48 (dd, 1H), 7 81 (s, 2H), 8 49 (d, 1H), 9 64 (s, 1H), m/z 412

Example 132

2-[3-Chloro-4-(hydroxyacetyl)piperazin-1-yl]anilino-4-(1-isopropyl-2-methyl-1*H*-imidazol-5 yl)pyrimidine

To a solution of 2-(3-chloro-4-piperazin-1 yl)anilino-4-(1-isopropyl-2-methyl-1*H* imidazol-5-yl)pyrimidine hydrochloride (Example 131, 0 44g, 1 0mmol) in DCM DMF (14ml, 6 1) at 0°C was added glycolic acid (90mg, 1 2mmol), HOBt.$H_2$0 (0 16g, 1 2mmol) and DIPEA (1 4ml, 8 0mmol) EDAC (0 23g, 1 2mmol) was added at 0°C, then the mixture was stirred at ambient temperature for 43 hours The solution was diluted with DCM (40ml), then washed with water (3 x 50ml), 1 0 molar solution of KOH (50ml), brine (50ml) and water (50ml) The organic extract was dried and concentrated. The residue was purified by chromatography on silica gel with MeOH DCM (2 5 97 5) to yield the title compound as a pale yellow solid (0 13g, 28%) NMR. 1 19 (t, 1H), 1 48 (d, 6H), 2 58 (s, 3H), 3 01 (m, 4H), 3 44 (m, 2H), 3 83 (m, 2H), 4 21 (s 2H), 5 57 (septet, 1H), 6 90 (d, 1H), 6 95 (d, 1H), 7 37 (m, 3H), 7 74 (s, 1H), 8 34 (d, 1H), m/z 470

Example 133

2-(3-Chloro-4-piperazin-1-yl)anilino-4-(1-isopropyl-2-methyl-1*H*-imidazol 5-yl)-5-fluoropyrimidine hydrochloride

The title compound was prepared from 2-[3-chloro-4-(4-acetylpiperazin-1-yl)anilino]-4-(1-isopropyl-2-methyl-1*H* imidazol-5-yl)-5 fluoropyrimidine (Example 117, 4 1g, 9 1mmol) by the method of Example 131, and isolated as a brown solid (1 5g, 94%) NMR 1 40 (d, 6H), 3 09 (m, 4H), 3 15 (s, 3H), 3 18 (m, 4H), 3 29 (m, 1H), 5 37 (septet, 1H), 7 14 (d, 1H), 7 36 (d, 1H), 7 54 (dd, 1H), 7 78 (d, 1H), 8 54 (d, 1H), 9 58 (s, 1H), m/z 430

Example 134

2-[3-Chloro-4-(4-hydroxyacetylpiperazin-1-yl)anilino]-4-(1 isopropyl-2-methyl-1*H* imidazol-5-yl)-5-fluoropyrimidine

The title compound was prepared from 2-(3-chloro-4-piperazin-1-yl)anilino-4-(1-isopropyl-2-methyl-1*H* imidazol-5 yl)-5 fluoropyrimidine hydrochloride (Example 133, 0 40g, 0 86mmol) by the method of Example 132, and purified by chromatography on silica gel with MeOH DCM (5 95) to yield a yellow solid (0 25g, 60%) NMR. 1 47 (d, 6H), 2.61 (s, 3H), 3 01 (m, 4H), 3 44 (m, 2H), 3 84 (m, 2H), 4 22 (s, 2H), 5 55 (septet, 1H), 6 96 (d, 1H), 7 22 (s, 1H), 7 36 (dd, 1H), 7 57 (d, 1H), 7 65 (d, 1H), 8 26 (d, 1H), m/z 488

Example 135

2-(3-Chloro-4-{4-[(2*S*)-1-oxopropan 2-ol]piperazin 1-yl}anilino)-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine

The title compound was prepared from 2-(3-chloro-4-piperazin-1-yl)anilino-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine hydrochloride (Example 133 0 40g, 0 86mmol) by the method of Example 38 The reaction mixture was evaporated under reduced pressure The residue was diluted with water (60ml) and extracted with DCM (3 x 50ml) The combined organic phases were washed with water (100ml), then dried and concentrated. The residue was purified by chromatography on silica gel with MeOH DCM (5 95) to yield the title compound as a yellow solid (0 35g, 88%) NMR. 1 39 (d, 3H), 1 46 (d, 6H), 2 60 (s, 3H), 2 80 (s, 1H), 3 01 (m, 4H), 3 60 (m, 2H), 3 77 (m, 1H), 3 79 (m, 1H), 4 52 (q, 1H), 5 51 (septet, 1H), 6 96 (d, 1H) 7 37 (dd, 1H), 7 58 (d, 1H), 7 59 (s, 1H), 7 68 (d, 1H), 8 27 (d, 1H), m/z 502

Example 136

2-[3-Chloro-4-(4-methoxyacetyl)piperazin-1-yl]anilino-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine

The title compound was prepared from 2-(3-chloro-4-piperazin-1-yl)anilino-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine hydrochloride (Example 133, 0.40g, 0.86mmol) by the method of Example 38. The reaction mixture was evaporated under reduced pressure. The residue was diluted with water (100ml) and extracted with chloroform (3 x 100ml). The combined organic phases were concentrated under reduced pressure, then diluted with EtOAc (100ml) and washed with water (150ml), then dried and concentrated. The residue was triturated with ether and the solid was purified by chromatography on silica gel with MeOH : DCM (5:95) to yield the title compound as a yellow solid (0.27g, 62%). NMR: 1.40 (d, 6H), 2.70 (s, 3H), 2.81 (m, 4H), 3.22 (s, 3H), 3.46 (m, 4H), 4.03 (s, 2H), 5.17 (septet, 1H), 7.03 (d, 1H), 7.24 (dd, 1H), 7.72 (d, 1H), 7.95 (s, 1H), 8.69 (s, 1H), 9.78 (s, 1H), m/z 502

Example 137

1-(4-{[5-fluoro-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-yl]amino}phenyl)azetidin-3-ol

(2*Z*)-3-(Dimethylamino)-2-fluoro-1-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one (Method 14, 1.54g, 6.46mM) and *N*-[4-(3-hydroxyazetidin-1-yl)phenyl]guanidine bicarbonate salt (Method 39, 2.3g, 9.7mM) were stirred and heated in 2-methoxyethanol (17ml) under nitrogen at 130°C for 24 hours. The solvent was removed in vacuo and the residue was partitioned between DCM and water. The organic layer was washed with water, dilute sodium bicarbonate, water, saturated sodium chloride and then dried with anhydrous sodium sulphate filtered and evaporated. The crude product was purified by silica chromatography eluting with MeOH:DCM (5:95). The product off the column was triturated with ether, filtered washed with the same solvent and dried to give the title compound as a brown solid (886mg, 18.3%). NMR: 1.35 (d, 6H), 2.5 (s, 3H + H_2O peak) 3.4 (t, 2H), 4.0 (t, 2H), 4.5 (q, 1H), 5.42 (m, 1H), 5.53 (d, 1H), 6.37 (d, 2H), 7.28 (m, 3H), 8.4 (d, 1H), 9.07 (s, 1H), m/z 383

Example 138

1-(4-{[5-Fluoro-4-(1-isopropyl-2-methyl-1*H*-imidazol 5-yl)pyrimidin-2-yl]amino}phenyl)azetidin 3-yl methanesulfonate

To an ice cooled solution of 1-(4-{[5-fluoro-4-(1-isopropyl-2-methyl-1*H* imidazol-5-yl)pyrimidin-2-yl]amino}phenyl)azetidin-3-ol (Example 137, 0 728g, 1 905mM) and triethylamine (153µl, 2 09mM) in dry DCM (22ml), mesyl chloride (162µl, 2 09mM) was added. The reaction was stirred at 0°C for 30 minutes and at room temperature for 20 hours The reaction mixture was diluted with more DCM and extracted in turn with water (twice), saturated sodium chloride, dried with anhydrous sodium sulphate, filtered and evaporated to give the title compound as a brown foam (717mg, 82%) NMR 1 37 (d, 6H), 2 48 (s, 3H +DMSO), 3 25 (s, 3H), 3 82 (m, 2H), 4 2 (m, 2H), 5 4 (m, 2H), 6 45 (d, 2H), 7 35 (m, 3H), 8 42 (d, 1H), 9 13 (s, 1H), m/z 461

Example 139

N-[4-(3-Azidoazetidin 1-yl)phenyl]-5-fluoro-4-(1 isopropyl 2 methyl-1*H*-imidazol-5 yl)pyrimidin-2-amine

To a solution of 1-(4-{[5 fluoro-4-(1-isopropyl-2-methyl 1*H*-imidazol-5 yl)pyrimidin-2-yl]amino}phenyl)azetidin-3 yl methanesulfonate (Example 138, 876mg, 1 90mM) in dry DMF (7 3ml) sodium azide (619mg, 9 5mM) was added. The reaction was stirred and heated at 80°C under nitrogen for 18 hours The reaction mixture was diluted with EtOAc and the solution extracted with water (twice), saturated sodium chloride and then dried with anhydrous sodium sulphate filtered and evaporated. The crude product was purified by silica chromatography eluting with MeOH DCM (2 98) to give the title compound as a brown foam (389mg, 50%) NMR 1 4 (d, 6H), 2 53 (s, 3H + DMSO), 3 65 (m, 2H), 4 1 (m, 2H), 4 44 (m, 1H), 5 4 (m, 1H), 6.44 (d, 2H), 7 33 (m, 3H), 8 35 (d, 1H), m/z 408

Example 140

N-[4-(3-Aminoazetidin 1-yl)phenyl] 5-fluoro-4-(1 isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin 2-amine

To a solution *N*-[4-(3-azidoazetidin-1-yl)phenyl]-5 fluoro-4-(1-isopropyl 2-methyl-1*H*-imidazol-5-yl)pyrimidin 2-amine (Example 139, 382mg, 938mM) in THF (10ml), triphenylphosphine (260mg, 0 984mM) was added. The reaction was stirred at room temperature under nitrogen for 24 hours Water (2 0ml) was then added and the mixture

stirred and heated at 65°C for 3 hours. Hydrochloric acid (1M, 1.5ml) was added and the THF removed in vacuo. More water was then added and the solution extracted with EtOAc. Sodium hydroxide (1M, 1.5ml) was added to the water layer and the solution was extracted with EtOAc. The organic layers were combined, dried with anhydrous sodium sulphate, filtered and evaporated to give the title compound as a yellow foam (324mg, 91%). NMR (DMSO-d_6 + d_4-acetic acid) 1.38 (d, 6H), 2.5 (s, 3H), 3.73 (m, 2H), 4.05 (m, 3H), 5.43 (m, 1H), 6.45 (d, 2H), 7.33 (s, 1H), 7.4 (d, 2H), 8.4 (d, 1H), m/z 382.

Example 141

N-[1-(4-{[5-Fluoro-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-yl]amino}phenyl)azetidin-3-yl] 2-hydroxyacetamide

To a mixture of *N*-[4-(3-aminoazetidin-1-yl)phenyl]-5-fluoro-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-amine (Example 140, 107mg, 0.28mM) and glycolic acid (26mg, 0.337mM) and HOBt hydrate (46mg, 0.337mM) in dry DCM (4.0ml), diisopropylamine (56µl, 0.337mM) and EDAC (65mg, 0.337mM) were added. The reaction was stirred at room temperature under nitrogen for 72 hours. The DCM was removed in vacuo and the residue dissolved in EtOAc and water. The layers were partitioned and separated. The organic layer was washed in turn with water, dilute sodium bicarbonate (twice), water, saturated sodium chloride and then dried with anhydrous sodium sulphate, filtered and evaporated. The residue was dissolved in MeOH (2.0ml) and 1.0 molar sodium hydroxide (0.25ml) added. The solution was stirred at room temperature for 1 hour. The reaction mixture was diluted with EtOAc and water and the layers partitioned and separated. The organic layer was washed with water, saturated sodium chloride, dried with anhydrous sodium sulphate, filtered and evaporated. The crude product was triturated with ether, filtered, washed with ether and dried to give the title compound as a yellow solid (79mg, 64%). NMR 1.38 (s, 6H), 2.5 (s, 3H + DMSO), 3.64 (t, 2H), 3.8 (d, 2H), 4.03 (t, 2H), 4.63 (m, 1H), 5.37 (t, 1H), 5.45 (m, 1H), 6.4 (d, 2H), 7.33 (m, 3H), 8.28 (d, 1H), 8.4 (d, 1H), 9.08 (s, 1H), m/z 440.

Example 142

N-[1-(4-{[5-Fluoro-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-yl]amino}phenyl)azetidin-3-yl]acetamide

To a stirred solution of *N*-[4-(3-aminoazetidin-1-yl)phenyl]-5-fluoro-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-amine (Example 140, 110mg, 0.29mM) and

triethylamine (44µl, 0 317mM) in dry DCM (4 0ml), acetic anhydride (30µl, 0 317mM) was added. The reaction was stirred at room temperature under nitrogen for 2 5 hours. A few drops of MeOH were added and the solution stirred for 10 minutes The reaction mixture was then diluted with more DCM and the solution extracted in turn with water (twice) and saturated sodium chloride The organic layer was then dried with anhydrous sodium sulphate, filtered and evaporated. The crude product was triturated with ether, filtered washed with ether and dried to give the title compound as a yellow solid (99mg, 81%) NMR 1 4 (d, 6H) 1 8 (s, 3H), 2 5 (s, 3H + DMSO), 3 5 (t, 2H), 4 05 (t, 2H), 4 53 (m, 1H), 5 43 (m, 1H), 6 4 (d, 2H), 7 33 (m, 3H), 8 42 (m, 2H) 9 08 (s, 1H), m/z 424

Example 143

N-[1-(4-{[5-Fluoro-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-yl]amino}phenyl)azetidin-3-yl]methanesulfonamide

To a stirred solution of *N*-[4-(3-aminoazetidin 1 yl)phenyl]-5-fluoro-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-amine (Example 140,110mg, 0 29mM) and triethylamine (44µl, 0 317mM) in dry DCM (4 0ml), methanesulphonyl chloride (25µl, 0 317mM) was added. The reaction was stirred at room temperature under nitrogen for 24 hours The reaction was filtered and the filtered solid washed with DCM This solid which was pure product was retained. The filtrate was taken and more DCM added. The solution was washed in turn with water (twice), saturated sodium chloride and then dried with anhydrous sodium sulphate, filtered and evaporated. The product so obtained was combined with the 1st batch of product and both were triturated with ether, filtered, washed with ether and dried to give the title compound as a yellow solid. NMR 1 4 (d, 6H), 2 6 (s, 3H), 2 9 (s, 3H), 3 55 (t, 2H), 4 13 (t, 2H), 4 25 (m, 1H), 5 37 (m, 1H), 6 4 (d, 2H), 7 33 (d, 2H), 7 58 (d, 1H), 7 75 (d, 1H), 8 5 (d, 1H), 9.22 (s, 1H), m/z 460

Example 144

(3-Chloro-4-morpholin-4-yl phenyl)-[4-(3-isopropyl-2 methyl-3*H*-imidazol-4-yl)-pyrimidin-2-yl]-amine

The title compound was prepared using the procedure described in Example 112, employing *N*-(3-chloro-4-morpholin-4-yl-phenyl)-guanidine carbonate (Method 17, 500mg, 1 97mmol), and (2*E*)-3-(dimethylamino)-1-(1-isopropyl 2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one (Method 24 of WO 03/076436, 363mg, 1 64mmol) Yield. 412mg, 61% as a white

solid. NMR. 1 42 (d, 6H), 2 47 (s, 3H), 2 90 (t, 4H), 3 72 (t, 4H), 5 60 (m, 1H), 7 02 (d, 1H) 7 10 (d, 1H), 7 40 (s, 1H), 7 54 (dd, 1H), 7 78 (d, 1H), 8 37 (d, 1H), 9 43 (s, 1H), m/z 413

Example 145

(3-Chloro-4-morpholin-4-yl phenyl)-[5 fluoro-4-(3 isopropyl-2-methyl 3*H*-imidazol-4-yl)-pyrimidin-2-yl]-amine

The title compound was prepared using the procedure described in Example 112, employing *N*-(3-chloro-4 morpholin-4-yl phenyl)-guanidine carbonate (Method 17, 500mg, 1 97mmol), and (2*Z*)-3-(dimethylamino)-2-fluoro-1-(1-isopropyl-2-methyl-1*H*-imidazol 5-yl)prop 2-en 1-one (Method 14, 392mg, 1 64mmol) Yield 203mg, 30% as a white solid, NMR. 1 41 (d, 6H), 2 49 (s, 3H), 2 90 (t, 4H), 3 72 (t, 4H), 5 35 (m, 1H), 7 10 (d, 1H), 7 34 (d, 1H) 7 50 (dd, 1H), 7 73 (d, 1H), 8 52 (d, 1H), 9 51 (s, 1H), m/z 431

Example 146

N-{4-[(2*RS*,6*SR*)-2,6-Dimethylmorpholin-4-yl]phenyl}-5-fluoro-4-(1-isopropyl 2-methyl-1*H* imidazol-5 yl)pyrimidin-2-amine

(2*E*)-3-(Dimethylamino) 1 (1-ethyl 2-methyl-1*H*-imidazol-5-yl)-2-fluoroprop-2-en-1-one (Method 15, 327mg, 1.37mmol) and *N* [4-(cis-2,6-dimethylmorpholino)phenyl]guanidine bicarbonate salt (Method 20, 510mg, 1 65mmol) in 2 methoxyethanol (8ml) were heated for 17 hours at 110°C The reaction mixture was evaporated under reduced pressure and the residue purified by chromatography on silica gel with MeOH DCM EtOAc (4 48 48) to (10 45 45) to give the title compound, after trituration with isohexane, as a solid (274mg 47 2%) NMR ($CDCl_3$) 1 26 (d, 6H), 1 44 (d, 6H), 1 68 (s, 2H), 2 39 (t, 2H), 2 58 (s, 3H), 3 39 (d, 2H), 3 82 (m, 2H), 5 57 (sept, 1H), 6 82 (s, 1H), 6 89 (d, 2H), 7 37 (d, 2H), 7 57 (d, 1H), 8 22 (d, 1H) m/z 425

Example 147

(R)-1 {4-[4-(3-Isopropyl-2-methyl-3*H* imidazol-4-yl)-pyrimidin-2-ylamino]-phenyl}-pyrrolidine-2-carboxylic acid cyclopropylamide

(R)-1-(4-Guanidino-phenyl)-pyrrolidine-2-carboxylic acid cyclopropylamide (Method 63, 0.29g, 1 0 mmol) and ((2*E*)-3-(dimethylammo)-1-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one, (Method 24 of WO 03/076436, 0 15g, 0 68 mmol) were added to 2-methoxyethanol (4 ml) and heated at 200°C for 2 hours in the microwave The solvent was

removed *in vacuo* and the gum was carefully chromatographed eluting with DCM, 1%MeOH/DCM, 2%MeOH/DCM and finally 3%MeOH/DCM to yield a yellow solid (110mg, 36%) NMR (299 954 MHz, $CDCl_3$) 8 28 (d, 1H), 7 39 (d, 1H) 7 34 (s, 1H), 6 85 - 6 82 (m, 2H), 6 60 6 57 (m, 3H), 5 61 (septet, 1H), 3 96 - 3 92 (m, 1H), 3 62 (t, 1H), 3 19 (q, 1H), 2 76 - 2 67 (m, 1H), 2 56 (s, 3H), 2 30 - 2 22 (m, 2H), 2 07 - 1 84 (m, 2H), 1 47 (d, 6H), 0 78-0 70 (m, 2H), 0 45-0 38 (m, 2H) m/z 446

Example 148

N-(3-Fluoro-4-morpholin-4-ylphenyl)-4-(1-isopropyl-2-methyl 1*H*-imidazol-5-yl)pyrimidin-2-amine

(2*E*)-3-(Dimethylamino)-1-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one (Method 24 of WO 03/076436) (330mg, 1 5mmol) and *N*-(3-fluoro-4-morpholinophenyl)guanidine bicarbonate salt (Method 23, 540mg, 1 8mmol) in 2-methoxyethanol (10ml) were heated for 49 hours at 100°C The reaction mixture was evaporated under reduced pressure and the residue purified by chromatography on silica gel with MeOH DCM (2 98 to 6 94) to give the title compound, after trituration with ether, as a solid (296mg 50%) NMR ($CDCl_3$) 1 51 (d, 6H), 2 59 (s, 3H), 3 06 (t, 4H), 3 89 (t, 4H), 5 68 (sept, 1H), 6 91 (m, 2H), 7 08 (m, 2H), 7 38 (s, 1H), 7 57 (dd, 1H), 8 32 (d, 1H) m/z 397

Example 149

5 Fluoro-*N*-(3-fluoro-4-morpholin-4-ylphenyl)-4-(1-isopropyl 2-methyl-1*H*-imidazol-5 yl)pyrimidin-2-amine

(2*E*)-3 (Dimethylamino)-2-fluoro-1-(1-isopropyl 2-methyl-1*H* imidazol-5-yl)prop-2 en-1-one (Method 14, 360mg, 1 5mmol) and *N*-(3-fluoro-4-morpholinophenyl)guanidine bicarbonate salt (Method 23, 540mg, 1 8mmol) in 2-methoxyethanol (10ml) were heated for 45 hours at 100°C The reaction mixture was evaporated under reduced pressure and the residue purified by chromatography on silica gel with MeOH DCM (3 97) to give the title compound, after trituration with ether, as a solid (298mg 48%) NMR ($CDCl_3$) 1 50 (d, 6H), 2 60 (s, 3H), 3 05 (t, 4H), 3 88 (t, 4H), 5 58 (sept, 1H), 6 90 (m, 2H), 6 95 (d, 1H), 7 08 (dd, 1H), 7 49 (dd, 1H), 7 59 (d, 1H), 8 26 (d, 1H), m/z 415

Example 150

(R)-1-{4-[5-Fluoro-4-(3-isopropyl-2-methyl-3*H*-imidazol-4-yl)-pyrimidin-2-ylamino]-phenyl} pyrrolidine-2-carboxylic acid cyclopropylamide

(*R*)-1-(4-Guanidino-phenyl) pyrrolidine-2-carboxylic acid cyclopropylamide (Method 63) (0 36g, 1 25mmol) and (2*Z*)-3-(dimethylamino)-2-fluoro-1-(1-isopropyl-2 methyl-1*H*-imidazol-5-yl)prop-2-en-1-one (Method 14, 0 15g, 0 63mmol) were added to 2-methoxyethanol (4 ml) and heated at 200°C for 2 hours in the microwave The solvent was removed *in vacuo* and the gum was carefully chromatographed eluting with DCM, 1%MeOH/DCM, 2%MeOH/DCM and finally 3%MeOH/DCM to yield a yellow solid (180mg, 62%) NMR (400 132 MHz, $CDCl_3$) 8.21 (d, 1H), 7 56 (d, 1H), 7 34 (d, 2H) 6 80 (s, 1H), 6 59 (m, 3H), 5 55 (septet, 1H), 3 62 (t, 1H), 3 21 3 15 (m, 1H), 2 74 - 2 68 (m, 1H), 2 58 (s, 3H), 2 28 - 2.22 (m, 2H), 2 05 1 98 (m, 1H) 1 96 - 1 86 (m, 1H), 1 45 (d, 6H), 0 79 - 0 72 (m, 2H), 0 44 - 0 37 (m, 2H), m/z 464

Example 151

N-[(3*R*)-1-(4-{[5-Fluoro-4-(1-isopropyl 2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-yl]amino}phenyl)pyrrolidin 3-yl]acetamide

4-((3*R*)-Acetamidopyrrolidin 1 yl) phenyl guanidine carbonate (Method 45, 1 25g, 4 28 mmol) and (2*Z*)-3-(dimethylamino)-2-fluoro-1 (1-isopropyl-2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one (Method 14, 0 79g, 3 3 mmol) in 2–methoxyethanol (20ml) were heated at 115°C for 18 hours under nitrogen. After evaporation under reduced pressure, chromatography on silica gel with MeOH/DCM (100 to 2 5 97 5) gave the title compound, after ether trituration, as a tan solid (612mg, 43%) NMR 1 38 (d, 6H), 1 80 (s, 3H), 1 80 – 1 92 (m, 1H), 2 12 – 2 26 (m, 1H) 2 49 (s, 3H), 2 97 – 3 03 (m, 1H), 3 14 – 3 25 (m, 1H), 3.29 – 3 49 (m, 2H), 4 3 – 4 41 (m, 1H) 5.20 – 5 32 (m, 1H), 6 50 (d, 2H), 7 30 (s, 1H), 7 32 (d, 2H), 8 09 (d, 1H), 8 39 (s, 1H), 9 05 (s, 1H), m/z 438

Example 152

N [(3*S*)-1-(4-{[5-Fluoro-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-yl]amino}phenyl)pyrrolidin-3-yl]acetamide

The title compound was prepared by an identical procedure to Example 151 above, but using 4-((3*S*)-acetamidopyrrolidin-1-yl) phenyl guanidine carbonate (Method 51) NMR 1 37 (d, 6H), 1 81 (s, 3H), 1 78 – 1 92 (m, 1H), 2 11 – 2 22 (m, 1H), 2 44 (s, 3H), 2 94 – 3 06 (m,

1H), 3 14 – 3 49 (m, 3H), 4 29 – 4 41 (m, 1H), 5 40 – 5 43 (m, 1H), 6 49 (d, 2H), 7 30 (s, 1H), 7 32 (d, 2H), 8 09 (d, 1H), 8 40 (d, 1H), 9 03 (s 1H), m/z 438

Example 153

N-{4-[(3S)-3-Aminopyrrolidin-1-yl]phenyl}-5-fluoro-4-(1-isopropyl 2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-amine

N-[(3S)-1-(4-{[5 Fluoro-4-(1 isopropyl 2-methyl 1*H*-imidazol-5-yl)pyrimidin-2-yl]amino}phenyl)pyrrolidin-3-yl]acetamide (Example 152, 0 49g, 1 12 mmol) in isopropanol (20ml), water (5ml) and hydrochloric acid (2 ml) was heated at reflux under nitrogen for 18 hours After evaporation under reduced pressure, the mixture was dissolved in water (15ml) and adjusted to pH 9 with aqueous ammonium hydroxide solution The solution was extracted with DCM (3 x 15 ml), dried and after evaporation under reduced pressure to give the title compound as a solid (0 42g, 95%) NMR. 1 38 (d, 6H), 1 61 – 1 73 (m, 1H), 2 00 –2 13 (m, 1H), 2.44 (s, 3H), 2 80 – 2 88 (m, 1H) 3 12 – 3 20 (m, 1H), 3 20 – 3 42 (m, 2H), 3 49 – 3 60 (m, 1H), 5 40 – 5 51 (m, 1H), 6 46 (d, 2H), 7.30 (d, 2H), 7 33 (s, 1H), 8 40 (s, 1H), 9 00 (s, 1H), m/z 396

Example 154

(2*S*)-*N*-[(3*S*)-1-(4-{[5-Fluoro-4-(1-isopropyl 2-methyl-1*H*-imidazol-5-yl)pyrimidin 2-yl]amino}phenyl)pyrrolidin 3-yl] 2-hydroxypropanamide

N-{4-[(3*S*)-3-Aminopyrrolidin 1-yl]phenyl}-5-fluoro-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-amine (Example 153, 220mg, 0 556 mmol), L – lactic acid (61mg, 0 667 mmol), HOBt mono hydrate (103mg, 0 667 mmol) and Hunig s base (0 12ml, 0 667mmol) in DCM (5ml) were reacted with EDAC (128mg, 0 667mmol) at room temperature under nitrogen for 18 hours The mixture was diluted with DCM (20ml) and washed with water (20ml), 1 N aqueous potassium hydroxide (20ml) and saturated aqueous sodium chloride (15ml) The mixture was dried and after evaporation under reduced pressure purified by HPLC on a Phenomenex column, (0-50% acetonitrile/water, 0 2% TFA) The fractions were diluted with water (20ml), basified with solid potassium carbonate, and extracted twice with EtOAc/DCM (2oml, 2 1) The solution was washed with saturated aqueous sodium chloride (15ml), dried and after evaporation under reduced pressure gave the title compound as a yellow solid, (79mg, 30%) NMR. 1 20 (d, 3H), 1 37 (d, 6H), 1 90 – 2 04 (m, 1H), 2 11 – 2.27 (m, 1H), 2 47 (s, 3H), 3 00 – 3 09 (m, 1H), 3 20 – 3 47 (m, 3H), 3 91 –

4 00 (m, 1H), 4 32 – 4 47 (m, 1H), 5 38 (s, 1H), 5 40 – 5 49 (m, 1H) 6 49 (d, 2H), 7 30 (s, 1H), 7 32 (d, 2H), 7 76 (d, 1H), 8 40 (d, 1H), 9 06 (s, 1H), m/z 468

Example 155

N-[(3*S*)-1-(4-{[5-Fluoro-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-yl]amino}phenyl)pyrrolidin-3-yl]-2-hydroxyacetamide

The title compound was prepared (38mg, 15%), using a procedure analogous to Example 154, starting from *N* {4-[(3*S*)-3-aminopyrrolidin-1-yl]phenyl}-5-fluoro-4-(1-isopropyl 2-methyl-1*H* imidazol 5-yl)pyrimidin 2-amine (Example 153 220mg, 0 556 mmol) and glycolic acid (51mg, 0 667 mmol) NMR 1 39 (d, 6H), 1 91 – 2 04 (m, 1H), 2 13 – 2 25 (m, 1H), 2 44 (s, 3H), 3 04 – 3 12 (m, 1H), 3 18 – 3 47 (m, 3H) 3 80 (d, 2H), 4 38 – 4 47 (m, 1H), 5 32 (t, 1H), 5 40 – 5 52 (m, 1H), 6 50 (d, 2H), 7 30 (s, 1H), 7 35 (d, 2H), 7 82 (d, 1H), 8 40 (d, 1H), 9 04 (s, 1H), m/z 454

Example 156

N-{4-[(3*R*)-3-Aminopyrrolidin 1-yl]phenyl}-5 fluoro-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-amine

The title compound was prepared in identical fashion, (0 45g, 99%), to Example 153 starting from *N* [(3R)-1-(4-{[5-fluoro-4-(1 isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2 yl]amino}phenyl) pyrrolidin 3-yl]acetamide (Example 151) NMR 1 36 (d, 6H), 1 61 – 1 76 (m, 1H), 2.00 – 2 16 (m, 1H), 2 47 (s, 3H), 2 79 – 2 89 (m, 1H), 3 14 – 3 41 (m, 3H), 3 28 (brs, 2H), 3 50 – 3 60 (m, 1H), 5 40 – 5 52 (m, 1H), 6 44 (d, 2H), 7 31 (d, 2H), 7 35 (s, 1H), 8 39 (d, 1H), 9 00 (s, 1H), m/z 396

Example 157

(2*S*)-*N*-[(3*R*)-1-(4-{[5-Fluoro-4-(1-isopropyl 2-methyl-1*H* imidazol-5 yl)pyrimidin 2 yl]amino}phenyl)pyrrolidin-3 yl]-2 hydroxypropanamide

The title compound was prepared (15mg, 6%), was prepared using a procedure analogous to Example 154 starting from *N*-{4-[(3*R*)-3-aminopyrrolidin-1-yl]phenyl}-5-fluoro-4-(1 isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-amine (Example 156, 220mg, 0 556 mmol) and L – lactic acid (61mg, 0 667 mmol) NMR 1 20 (d, 3H), 1 36 (d, 6H), 1 89 – 2 01 (m, 1H), 2 14 – 2 22 (m, 1H), 2.43 (s, 3H), 3 02 – 3 10 (m, 1H), 3 14 – 3 48 (m, 3H),

3 92 – 4 03 (m, 1H), 4 34 – 4 46 (m, 1H), 5 35 (d, 2H), 5 41 – 5 53 (m, 1H), 6 49 (d, 2H), 7 30 (s, 1H), 7 32 (d, 2H), 8 40 (d, 1H), 9 05 (s, 1H), m/z 468

Example 158

N-[(3*R*)-1-(4-{[5-Fluoro-4-(1-isopropyl 2-methyl-1*H*-imidazol-5-yl)pyrimidin-2-yl]amino}phenyl)pyrrolidin-3-yl]-2 hydroxyacetamide

The title compounds was prepared (38mg, 15%), was prepared using a procedure analogous to Example 155 starting from *N*-{4-[(3*R*)-3-aminopyrrolidin-1-yl]phenyl}-5-fluoro-4-(1 isopropyl-2-methyl 1*H* imidazol-5 yl)pyrimidin-2-amine (Example 156, 220mg, 0 556 mmol) and glycolic acid (51mg, 0 667 mmol) NMR. 1 39 (d, 6H), 1 92 – 2 04 (m, 1H), 2 14 – 2 26 (m, 1H), 2 44 (s, 3H), 3 04 – 3 13 (m, 1H), 3 18 – 3 49 (m, 3H), 3 80 (d, 2H), 4 46 – 4 51 (m, 1H), 5 34 (t, 1H), 5 42 – 5 51 (m, 1H), 6 49 (d, 2H), 7 31 (d, 1H), 7 35 (d, 2H), 7 82 (d, 1H), 8 41 (d, 1H), 9 06 (s 1H), m/z 454

Example 159

(*S*)-1-{4-[5-Fluoro-4-(3-isopropyl-2-methyl-3*H*-imidazol-4-yl)-pyrimidin-2-ylamino]-phenyl}-pyrrolidine-2-carboxylic acid dimethylamide

(S)-1-(4-Guanidino-phenyl)-pyrrolidine-2-carboxylic acid dimethylamide (Method 54, 0 5g, 1 82mmol) and (2*Z*)-3-(dimethylamino) 2-fluoro-1-(1-isopropyl 2-methyl-1*H*-imidazol-5-yl)prop-2-en-1-one (Method 14, 0.2g, 0 83mmol) were heated at reflux in butanol (7 ml) overnight. LCMS indicated only 7% product. The reaction was transferred to a microwave tube and heated at 200°C for 2 hours LCMS indicated 15% starting material and mainly product. The solvent was removed *in vacuo* and chromatographed. The product was purified by HPLC and the required fractions were combined and basified with K_2CO_3 (0 5 g), extracted with DCM (2 x 50 ml), dried and the solvent removed *in vacuo* to yield a yellow solid (101mg, 31%) NMR (400 132 MHz, $CDCl_3$) 8 18 (d, 1H), 7 56 (d, 1H), 7 24 (d, 2H), 6 69 (s, 1H), 6 42 (d, 2H), 5 59 (septet, 1H), 4 51 (dd, 1H), 3 64 (dt, 1H), 3 41 (q, 1H), 3 16 (s, 3H), 2 98 (s, 3H), 2 56 (s, 3H), 2 38 2 28 (m, 1H), 2 25 - 2 14 (m, 1H), 2 08 - 1 98 (m, 2H), 1 39 (t, 6H), m/z 452

Example 160

(R) 1-{4-[5-Fluoro-4-(3-isopropyl-2-methyl-3*H*-imidazol-4-yl)-pyrimidin-2-ylamino]-phenyl}-pyrrolidine-2-carboxylic acid methylamide

(R)-1-(4-Guanidino-phenyl) pyrrolidine-2-carboxylic acid methylamide (Method 59, 0 22g, 0 82mmol) and (2*Z*)-3-(dimethylamino)-2-fluoro-1-(1-isopropyl-2-methyl-1*H* imidazol-5-yl)prop-2-en-1-one (Method 14, 0 15g, 0 63mmol) were added to 2-methoxyethanol (4 ml) and heated at 200°C for 2 hours in the microwave Solvent was removed *in vacuo* and chromatographed. The product was passed purified by HPLC, and the required fractions were combined and basified with K_2CO_3 (0 5 g), extracted with DCM (2 x 50 ml), dried and solvent removed *in vacuo* to yield a yellow solid (110mg, 40%) NMR (400 132 MHz, $CDCl_3$) 8 21 (d, 1H), 7 56 (d, 1H), 7 34 (d, 2H), 6 79 (s, 1H), 6 60 (d, 2H), 6 56 (s, 1H), 5 56 (septet, 1H), 3 99 (t, 1H), 3 64 (t, 1H), 3 20 (q, 1H), 2 80 (d, 3H), 2 58 (s, 3H), 2 29 2 24 (m, 2H) 2 06 - 1 89 (m, 2H), 1 45 (d, 6H) m/z 438

Example 161

(R)-1-{4-[4-(3-Isopropyl-2-methyl-3H-imidazol-4-yl)-pyrimidin 2-ylamino]-phenyl}-pyrrolidine-2-carboxylic acid methylamide

(*R*)-1 (4-Guanidino-phenyl)-pyrrolidine-2-carboxylic acid methylamide (Method 59, 0 27g, 1 0 mmol) and of (2*E*)-3-(dimethylamino) 1-(1-isopropyl-2-methyl 1*H*-imidazol-5-yl)prop-2-en-1-one, (Method 24 of WO 03/076436, 0 15g, 0 0 68 mmol) were added to 2-methoxyethanol (4 ml) and heated at 200°C for 2 hours in the microwave The solvent was removed *in vacuo* and the gum was carefully chromatographed eluting with DCM, 1%MeOH/DCM, 2%MeOH/DCM and finally 3%MeOH/DCM to yield a yellow solid (101mg, 35%) NMR (400 132 MHz, $CDCl_3$) 8 28 (d, 1H), 7 39 (d, 2H), 7 34 (s, 1H), 6 89 (s, 1H), 6 83 (d, 1H), 6 61 - 6 57 (m, 3H), 5 62 (septet, 1H), 3 99 (t, 1H), 3 65 (t, 1H), 3 24 3 17 (m, 1H), 2 80 (d, 3H), 2 55 (s, 3H), 2 29 - 2 24 (m, 2H), 2 06 - 1 89 (m, 2H), 1 46 (d, 6H), m/z 420

Example 162

N-[(3*R*)-1-(4-{[4-(1-Isopropyl-2-methyl-1*H*-imidazol 5-yl)pyrimidin-2-yl]amino}phenyl)pyrrolidin-3-yl]acetamide

4-((3*R*)-Acetamidopyrrolidin-1-yl) phenyl guanidine trifluoroacetate salt (Method 70, 1 79g, 4 55mmol), (2*E*) 3-(dimethylamino)-1 (1-isopropyl-2-methyl-1*H* imidazol-5-yl)prop-

2-en-1-one (Method 24 of WO 03/076436, 1 01g, 4 55mmol) in 2-methoxyethanol (20ml) and DIPEA (1 74ml, 10mmol) were heated at 115°C for 20 hours under nitrogen After evaporation under reduced pressure, chromatography on silica gel with MeOH/DCM (100 to 5 95) gave the title compound, after ether trituration, as a yellow solid (165mg, 9%) NMR. 1 39 (d, 6H), 1 75 – 1 90 (m, 1H), 1 80 (s, 3H), 2 11 – 2 22 (m, 1H), 2 44 (s, 3H), 2 98 – 3 02 (m, 1H), 3 16 – 3 48 (m, 3H), 4 28 – 4 37 (m, 1H), 5 64 – 5 75 (m, 1H), 6 50 (d, 2H), 6 89 (d, 1H), 7 35 (s, 1H), 7 37 (d, 1H), 8 09 (d, H), 8 98 (s, H) m/z. 420

Example 163

N-[(3R)-1-(2-Fluoro-4-{[4-(1-isopropyl-2-methyl 1*H*-imidazol 5-yl)pyrimidin-2 yl]amino-2-fluoro}phenyl)pyrrolidin-3-yl]acetamide

The title compound (0 24g, 10%), was prepared by an analogous route to Example 162, starting from 2–fluoro-4-((3R)-acetamidopyrrolidin-1 yl) phenyl guanidine carbonate (Method 69, 1 16g, 5 23 mmol) and (2*E*)-3-(dimethylamino)-1-(1-isopropyl-2-methyl 1*H*-imidazol-5-yl)prop-2-en 1-one, (Method 24 of WO 03/076436, 2 43g, 7 84 mmol) NMR. 2 41 (d, 6H), 1 70 – 1 86 (m, 1H), 1 80 (s, 3H), 2 07 – 2 18 (m, 1H), 2 46 (s, 3H), 3 04 – 3 12 (m, 1H), 3 19 – 3 28 (m, 1H), 3 32 – 3 49 (m, 2H), 4 22 – 4 39 (m, 1H), 5 62 – 5 72 (m, 1H), 6 68 (t, 1H), 6 98 (d, 2H), 7 21 (d, 1H), 7 39 (s, 1H), 7 50 (d, 1H), 8 07 (d, 1H), 8 32 (d, 1H), 9 24 (s, 1H), m/z 438

Preparation of Starting Materials

Method 1

N-{4-[4-(Methylsulphonyl)piperazin-1-yl]phenyl}guanidine

1-Methylsulphonyl-4-(4-nitrophenyl)piperazine [J Med. Chem. 20 (8) 987-996 (1977)] (24g) in EtOH (250 ml) was hydrogenated over 10% Pd / carbon (2 4 g) at ambient temperature and pressure The reaction was filtered and the catalyst and insoluble solid were washed with MeOH 2N hydrochloric acid (100 100 ml) Evaporation under reduced pressure gave the aniline hydrochloride as an orange solid (19 8 g 81%) M/z 256

A mixture of the aniline (4 7g 16 1 mmol) and cyanamide (800 mg 19 0 mmol) in EtOH (25 ml) and 1 4-dioxane (25 ml) were heated at 90°C - 95°C for a total of 19 hours Extra cyanamide (450 mg) and EtOH (10 ml) were added after 5 5 hours The reaction mixture was evaporated under reduced pressure Water (100 ml) was added to the residue

before basifying with 40% sodium hydroxide (pH>11) The solid was filtered off, washed with a little cold water, dried on a filter then transferred to a beaker The residue was triturated with acetone (50 ml), filtered and air dried to give the title compound (3 2 g 58%) NMR. 2 89 (s, 3H), 3 08 (m, 4H), 3 21 (m, 4H), 3 30 (b s, 4H), 6 73 (d, 2H), 6 73 (d, 2H), m/z 298

Method 2

N-[4-(4-Acetylpiperazin 1-yl)phenyl]guanidine bicarbonate salt

1-Acetyl-4-(4-nitrophenyl)piperazine [J Med. Chem. 20 (8) 987 996 (1977)] (20 8 g) in EtOH (200 ml) was hydrogenated over 10% Pd / carbon (2 1 g) at ambient temperature and pressure. The catalyst was filtered off, washed with EtOH (500 ml) and evaporation under reduced pressure to give the aniline as a purple solid, 22g (still wet)

The aniline (5 0 g 22 8 mmol) was stirred in dry 1,4-dioxane (55 ml) and EtOH (20 ml) 4N HCl in dioxane (6 0 ml 25 mmol) was added then, after 3 to 4 minutes, cyanamide (1 6 g 38 1 mmol) and extra EtOH (4 ml) were added. The reaction was heated at 95°C for 17 5 hours then extra cyanamide (300 mg) and 4N HCl / dioxane (2 ml) were added. The reaction was continued with heating for 6 hours After evaporation under reduced pressure, the solid was triturated with ether (2x70 ml) and air dried. The solid was dissolved in water (40 ml), slowly added saturated sodium hydrogen carbonate solution (75 ml) with stirring After 21 hour, the solid was collected by filtration, washed with acetone (2x40 ml) and dried under vacuum. (5 7g 77%) NMR 2 01 (s, 3H), 2 98 (t, 2H), 3 05 (t, 2H), 2 9-3 8 (v b s, exchangeables), 3 54 (m, 4H), 6 81 (d, 2H), 6 88 (d, 2H), m/z 262

Method 3

(2*E*)-2-Chloro-3-(dimethylamino)-1-(1-isopropyl 2 methyl-1*H*-imidazol-5 yl)prop-2-en-1-one

Benzyltrimethylammonium dichloroiodate (2 6g 7 5mmol) was added in portions to a stirred solution of (2*E*) 3-(dimethylamino)-1-(1-isopropyl 2-methyl-1*H* imidazol-5-yl)prop-2-en-1-one (Method 24 of WO 03/076436, 1 1g 5mmol) in MeOH /DCM (15/30ml) at room temperature. After 1 hour water (10ml) and DCM (20ml) were added followed after a further 30 minutes by saturated sodium hydrogen carbonate solution (20ml) The organics were separated, re-extracted the aqueous with DCM (25ml) The combined organics were washed

with 5% (w/v) sodium thiosulphate solution (30 to 35ml) and brine (25ml), dried (Na_2SO_4) and evaporated to give the title compound as an oil (crude yield 1 68 g still wet) M/z 256

Method 4

N [4-(Morpholino)phenyl]guanidine bicarbonate salt

4-Morpholino aniline (1 78g 10mmol) and cyanamide (420mg 10mmol) were stirred in 1,4-dioxane (17 5ml) 7N HCl in 1,4-dioxane (2 5ml) was slowly added before heating at 95°C for 11 hours The reaction mixture was evaporated under reduced pressure and the solid triturated with ether before air-drying overnight. This solid was treated with water (20ml) and stirred during slow addition of saturated aqueous sodium hydrogen carbonate solution (15ml) The solid was collected by filtration, washed with acetone (15ml) and air dried to give the title compound 2 3g 80% NMR 2 95 (4H, m), 3 39 (exchangeables, v brs), 3 68 (4H, m), 6 68 (2H, d), 6 71 (2H, d), m/z 221

Method 5

2-Amino-5-chloro-4-(1-isopropyl 2-methyl-1*H*-imidazol-5-yl)pyrimidine

A solution of 2-amino-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)pyrimidine (Method 39 of WO 03/076436, 0 5g, 2 3mmol) and N-chlorosuccinimide (0 4g, 3mmol) in acetic acid (5 ml) was stirred at 65°C under nitrogen for 2 hours Then the reaction mixture was allowed to cool down to room temperature and the solvent was removed under vacuum. The crude was taken up in EtOAc and water then portions of solid potassium carbonate were added to this stirred biphasic solution until pH 8 9 was reached The two layers were separated, the aqueous layer was extracted once with EtOAc then the organics were combined, washed with brine and dried. Removal of the solvent left a residue, which was purified on silica (MeOH /DCM/EtOAc, from 0/50/50 to 6/47/47) Triturating the foam in ether gave a white solid, which was filtered off (0 49g, 85%) NMR ($CDCl_3$) 1 51 (d, 6H), 2 55 (s, 3H), 4 85 (septuplet, 1H), 5 01 (b s, 2H), 7 48 (s, 1H), 8 31 (s, 1H), m/z 252 (^{35}Cl), 254 (^{37}Cl) m/z 250 (^{35}Cl), 252 (^{37}Cl)

Method 6

4-[*N*-(Propionyl)-*N*-(isopropyl)amino] 5-methylisoxazole

Triethylamine (1 0eq) was added dropwise over 45mins to a solution of *N* isopropyl-5-methylisoxazol-4-amine (Method 1 of WO 03/76436, 258g, 1 0eq) and n-propionyl

chloride (1 0eq) in DCM (8 6vol.eq) at –3°C The reaction was then stirred at 0°C for 20mins and then left to warm to room temperature overnight Water (10vol eq) was added and the mixture was then stirred for 30mins. The organic layer was separated and washed with water (2 x 10vol eq), 2M HCl (3 x 10vol.eq), brine (10vol.eq), dried, filtered and the solvent was then removed *in vacuo* from the filtrate to leave a yellow oil which crystallised on standing (330g, 91%) NMR 0 91 (3H, t) 0 95 (6H, b s), 1 9 (2H, q), 2 35 (3H, s), 4 8 (1H, septuplet), 8 61 (1H, s)

Method 7

N-[(*E*)-1 Acetyl 2-aminoethenyl]-*N*-isopropylpropanamide

4-[*N*-(Propionyl)-*N*-(isopropyl)amino]-5 methylisoxazole (Method 6, 330g, 1 0eq) was stirred under hydrogen (1 0eq), with 10% palladium on carbon (0 1eq) in EtOH (10vol.eq) at 25°C overnight. The catalyst was removed by filtration and the EtOH was removed *in vacuo* to leave an off white solid (351g, 98%) This was used without further purification

Method 8

1 Isopropy 2 ethyl-5-acetylimidazole

N-[(*E*)-1-Acetyl-2-aminoethenyl]-*N*-isopropylpropanamide (Method 7, 373g, 1 0eq) was stirred with sodium hydroxide (1 4eq) in EtOH (4vol eq) The reaction was heated to reflux (85°C) and stirred overnight. Ammonium chloride (2 0eq) was then added and this was stirred for 2 hours (the consistency of the reaction changed to a fine precipitate) The reaction was then allowed to cool, the solid was filtered off and discarded, and the solvent was then removed *in vacuo* Acetone was then added to the residue, the solid was filtered off and discarded. The solvent was then removed *in vacuo* Prep chromatography was then performed by eluting with 5% MeOH / DCM, to leave a brown oil (290g, 86%) NMR 1 23 (3H, t), 1 43 (6H, d), 2 40 (3H, s), 2 77 (2H, q), 5 0 (1H, b s), 7 87 (1H, s)

Method 9

5-(3-Dimethylaminoprop-2-en-1 oyl)-1 isopropyl-2-ethylimidazole

1-Isopropy-2-ethyl 5-acetylimidazole (Method 8, 290g, 1 0eq) was stirred with DMF DMA (2 0eq) in DMF (15vol eq) The reaction was heated to 130°C and stirred overnight. The reaction was allowed to cool and the solvent removed *in vacuo* The residue was

triturated with ether and the brown solid filtered off, washed with ether, this process was repeated. The filtrates were then combined and purified by prep chromatography eluting with 5% MeOH / DCM to give a yellow solid (223g, 59%) NMR 1 24 (3H, t), 1 46 (6H, d), 2 73 (2H, q), 2 96 (6H, b s), 5 09 (1H, septuplet), 5 56 (1H, d), 7 51 (1H, s), 7 53 (1H, d)

Method 10

4-(*N*-Butyryl-*N*-ethylamino)-5 methylisoxazole

To a stirred, ice cooled solution of 4-ethylamino-5-methylisoxazole (Method 5 of WO 03/76436 49 6g, 305mM) and triethylamine (77 0g, 763mM, 107ml) in DCM (800ml), was slowly added a solution of n butyryl chloride (35 5, 333mM, 35ml) in DCM (100ml) There was a moderate exotherm. The solution was allowed to warm to ambient temperature and stir for 1 hour The reaction mixture was washed with water, 2N HCl, brine sat. $NaHCO_3$ and brine It was dried and the solvent was evaporated to give the title compound as an oil, which crystallized to a waxy solid (45 1g, 75%) NMR (300Mz, DMSO-d6) 0 78 (t, 3H), 0 96 (t, 3H) 1 44 (sext, 2H), 1 93 (t, 2H), 2 33 (s, 3H), 3 49 (q, 2H), 8 68 (s, 1H), m/z 197

Method 11

N-[(*E*)-1-Acetyl-2-aminoethenyl]-*N*-ethylbutanamide

A solution of 4-(*N* butyryl-*N* ethylamino)-5 methylisoxazole (Method 10, 45g, 230mM) in EtOH (1 5l) was hydrogenated over 10% Pd/C (11 25g) at 4 bar The catalyst was filtered off and the solution was evaporated. The residue was triturated with ether and the crystalline intermediate was filtered off (33 94g) This was used without further purification.

Method 12

1-Ethyl-2-propyl-5 acetylimidazole

A solution of *N*-[(*E*)-1 acetyl-2-aminoethenyl] *N*-ethylbutanamide (Method 11, 33 9g, 171mM) and NaOH (8.2g, 205mM) in EtOH (400ml) was heated under reflux for 4 hours NH_4Cl (11 9g, 222mM) was added to the hot solution, which was allowed to cool and stir for 48 hours The reaction mixture was filtered and the solution was evaporated. The residue was taken into ether and filtered again. The solution was evaporated to give the title compound as a yellow oil (30 55g, 74%) NMR (300Mz, DMSO-d6) 0 92 (t, 3H), 1 17 (t, 3H), 1 70 (sext, 2H), 2.37 (s, 3H), 2 64 (t, 2H), 4 23 (q, 2H), 7 83 (s, 1H), m/z 181

Method 13

5-(3-Dimethylaminoprop-2-en-1-oyl)-1-ethyl 2-propylimidazole

A solution of 1-ethyl-2-propyl 5-acetylimidazole (Method 12, 30 5g, 169mM) and DMF DMA (49 7g, 338mM, 58ml) in DMF (100ml) was stirred at 130°C for 18 hours, allowing distillation of the EtOH generated. On cooling, the product crystallized from the reaction mixture and was filtered and washed with ether (20 94g) A second crop was obtained on evaporating the solvent and triturating with ether (8 8g) (29 74g, 75%) NMR (300Mz, DMS0-d6) 0 92 (t, 3H), 1 18 (t, 3H), 1 70 (sext, 2H) 2 60 (t, 2H), 2 94 (brs, 6H), 4 30 (q, 2H), 5 56 (d, 1H), 7 50 (d, 1H), 7 56 (s, 1H) m/z 236

Method 14

(2Z)-3-(Dimethylamino)-2-fluoro-1-(1 isopropyl 2-methyl-1*H*-imidazol-5-yl)prop-2-en 1-one

To a stirred solution of (2*E*)-3-(dimethylamino)-1-(1-isopropyl-2 methyl-1*H*-imidazol-5 yl)prop-2-en 1-one, (Method 24 of WO 03/076436, 5 53g, 25mmol) in MeOH (100ml) at ambient temperature, was added in portions over ~5mins, Selectfluor (14 16g, 40mmol) The temperature was maintained at 25-30°C by slight cooling After stirring for 90min the reaction mixture was cooled in ice/acetone and filtered. The filtrate was evaporated under reduced pressure and the residue was taken into DCM. It was washed with aq ammonia, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure The title compound was isolated by MPLC on silica gel using two separate columns (10% EtOH / EtOAc, then 3 5% EtOH / DCM) as a golden viscose oil, which crystallized on standing over several weeks Yield = 2 50g (42%) NMR (300Mz) 1 40 (d, 6H), 2 38 (s, 3H), 3 05 (s, 6H), 4 70 (septet, 1H), 6 96 (d, 1H), 7 08 (s, 1H), ^{19}F NMR (376MHz) -166 7 (d), m/z 240

Method 15

(2Z)-3-(Dimethylamino)-1-(1-ethyl 2-methyl-1*H*-imidazol 5-yl)-2-fluoroprop-2-en-1-one

The title compound was prepared by the procedure of Method 14 above on a 46mM scale of (2*E*)-3-(dimethylamino)-1-(1 ethyl 2-methyl-1*H*-imidazol-5 yl)prop-2-en-1-one (Method 16 of WO 02/20512) The title compound was isolated by MPLC on silica gel using two separate columns (5% EtOH / DCM, then 10% EtOH / EtOAc) and crystallized readily on trituration with ether Yield =3 93g (38%) NMR (300Mz) 1 2 (t, 3H), 2 38 (s, 3H), 3 05 (s, 6H), 4 18 (q, 2H), 6 96 (d, 1H), 7 34 (s, 1H), ^{19}F NMR (376MHz) -168 2 (d), m/z 226

Method 16

(2Z)-1-(1 Cyclobutyl-2-methyl-1*H*-imidazol-5-yl)-3-(dimethylamino)-2-fluoroprop-2-en-1-one

The title compound was prepared from (2*E*) 1-(1-cyclobutyl 2-methyl-1*H*-imidazol-5-yl)-3-(dimethylamino)prop-2-en-1-one (Method 37 of WO 03/076435, 3 0g) by the procedure of Method 14 Purification by silica gel chromatography eluting with EtOH / EtOAc (5 95 to 10 90) afforded the title compound as a yellow oil (1 64g, 51%) NMR ($CDCl_3$) 1 73-1 88 (m, 2H), 2 47 (s, 3H), 2 45 2 55 (m, 4H), 3 10 (s, 6H), 5 00 (quintet, 1H), 6 87 (d, 1H), 7 23 (d, 1H), m/z 252

Method 17

N-(3-Chloro-4-morpholin-4-yl phenyl)-guanidine bicarbonate salt

The title compound was prepared using the procedure described above for Method 4 using *N*-(4-amino-2-chlorophenyl)morpholine (1 1g, 5 19mmol) cyanamide (273mg 6 49mmol), 4 0M HCl in dioxane (1 62ml, 6 49mmol) and dioxane (30ml) Yield. 820mg, 50% NMR. 2 85 (t, 4H), 3 70 (t, 4H), 6 73 (dd, 1H), 6 81 (d, 1H), 7 00 (d, 1H)

Method 18

1-(Cis-2,6-dimethylmorpholino)-4-nitrobenzene

1-Fluoro-4-nitrobenzene (4 9g, 34 75 mmol) was added to cis-2,6-dimethylmorpholine (44 4g, 38 26 mmol) and anhydrous potassium carbonate (2 5g, 18 12 mmol) in acetonitrile (50ml) The reaction was heated under reflux for 19 hours, cooled, filtered and the solid washed with acetonitrile. Evaporation of the filtrate gave the title compound as a yellow solid. (8 1g, 99%) NMR ($CDCl_3$) 1 28 (d, 6H), 2 61 (t, 2H), 3 66 (td, 2H), 3 76 (m, 2H), 6 82 (d, 2H), 8 13 (d, 2H), m/z 237

Method 19

4-(Cis-2,6-dimethylmorpholino)aniline

1-(Cis-2,6-dimethylmorpholino)-4-nitrobenzene (Method 18, 8g) in EtOH (100ml) was reduced with hydrogen over 10% palladium / carbon (800mg) at 50°C After filtering off the catalyst and washing with EtOH, evaporation of the filtrate gave the title compound as a red/brown oil, which started to solidify after several days (quantitative yield) NMR ($CDCl_3$) 1.23 (d, 6H), 2.33 (t, 2H), 3.25 (d, 2H), 3 81 (m, 2h), 6 65 (d, 2H), 6 79 (d, 2H), m/z 207

Method 20

N-[4-(Cis-2,6-dimethylmorpholino)phenyl]guanidine bicarbonate salt

4-(Cis-2,6-dimethylmorpholino)aniline (Method 19, 6g, 29 10mmol) and cyanamide (1 5g, 35 71mmol) were stirred in 1,4-dioxane (45ml) 4N HCl in 1,4-dioxane (8 8ml, 35 2mmol) was slowly added before heating at 100°C for 1 75 hours. The reaction mixture was evaporated under reduced pressure and the residue triturated with ether The resulting gum was treated with water (30ml) and stirred during slow addition of saturated aqueous sodium hydrogen carbonate solution (40ml) The solid was collected by filtration, washed with acetone (2x25ml) and air dried to give the title compound (6 4g 71%) NMR 1 15 (d, 6H), 2.21 (t, 2H), 3.48 (td, 2H), 3 68 (m, 2H) 6 85 (d, 2H), 6 89 (brd, 2H), m/z 249

Method 21

1-Fluoro-2-morpholino-5-nitrobenzene

1,2-Difluoro-4-nitrobenzene (8 0g, 50 mmol) was added to morpholine (4 85g, 55 7 mmol) and anhydrous potassium carbonate (3 85g, 27 9 mmol) in acetonitrile (75ml) The reaction was heated at 85°C for 3 hours, cooled, filtered and the solid washed with EtOAc (50ml) Evaporation of the filtrate, trituration with isohexane and filtration gave the title compound as a solid (11 2g, 98%) NMR ($CDCl_3$) 3 28 (t, 4H), 3 88 (t, 4H), 6 92 (t, 1H), 7 92 (dd, 1H), 8 00 (m, 1H), m/z 227

Method 22

3-Fluoro-4-morpholinoaniline

1-Fluoro-2-morpholino-5-nitrobenzene (Method 21, 9g) in EtOH EtOAc (50 50ml) was reduced with hydrogen over 10% palladium / carbon (800mg) After filtering off the catalyst and washing with EtOH, evaporation of the filtrate gave the title compound as a brown solid (quantitative yield) NMR ($CDCl_3$) 2 96 (t, 4H), 3 55 (bra, 2H), 3 84 (t, 4H), 6 41 (d/s, 2H), 6 79 (t, 1H), m/z 197

Method 23

N-(3 Fluoro-4-morpholinophenyl)guanidine bicarbonate salt

3-Fluoro-4-morpholinoaniline (Method 22, 7 8g, 39 8mmol) and cyanamide (2 1g, 50mmol) were stirred in 1,4-dioxane EtOH (75 7 5ml) 4N HCl in 1,4-dioxane (11 9ml, 47 6mmol) was slowly added before heating at 95°C for 6 hours. The reaction mixture was

evaporated under reduced pressure and the residue triturated with ether The resulting solid was treated with water (35ml) and stirred during slow addition of saturated aqueous sodium hydrogen carbonate solution (60ml) The solid was collected by filtration, washed with cold water (10ml) then acetone (2x25ml) and air dried to give the title compound (10 9g 91%) NMR 2 90 (t, 4H), 3 72 (t, 4H) 5 24 (brs, 4H), 6 52 (d/s, 1H), 6 54 (t, 1H), 6 87 (t, 1H), m/z 239

Method 24

1-Acetyl-4-(2-chloro-4-nitrophenyl)piperazine

2-Chloro-1-fluoro-4-nitrobenzene (10g, 57mmol) and 1-acetylpiperazine (14 6g, 114mmol) were heated neat at 55°C for 1h Then the reaction mixture was allowed to cool down to room temperature. The viscous orange solution was diluted with EtOAc and water The organics were washed with water (3 times), brine, dried and evaporation of the solvent gave an orange oil which was triturated with isohexane After evaporation of solvent the title compound was obtained as a yellow solid which was dried overnight in vac oven at 50°C (15 68g, 97%) It was used without further purification NMR (400.MHz) 2 03 (d, 3H), 3 18 (dt, 4H), 3 62 (m, 4H), 7 30 (d, 1H) 8 17 (dd, 1H), 8 26 (d, 1H) m/z 284-286

Method 25

1 Acetyl-4-(2-methyl-4-nitrophenyl)piperazine

1 Butyl-3 methylimidazolium tetrafluoroborate (1 75g, 7 74mmol) was added to a stirred solution of 1-fluoro-2-methyl-4-nitrobenzene (12g, 77 35mmol) and 1-acetylpiperazine (39 7g, 309 4mmol) in acetonitrile (3ml) The reaction mixture was then heating at 95°C overnight. The reaction mixture was allowed to cool down to room temperature. The solution was diluted with EtOAc and water The precipitate formed was filtered off to give a solid corresponding to the required product. The organics were washed with water (4 times), brine, dried and evaporation of solvent to give a solid. Both solids were combined and after trituration with isohexane/ether and filtration, the title compound was obtained as a yellow solid which was dried in vac oven overnight at 50°C (19 61g, 96%) NMR (400MHz) 2 06 (s, 3H), 2 38 (s, 3H), 2 99 (dt, 4H), 3 61 (m, 4H), 7 14 (d, 1H), 8 04 (dd, 1H), 8 07 (d, 1H), m/z 264

Method 26

1-Acetyl-4-(2-fluoro-4-nitrophenyl)piperazine

A stirred solution of 1-(2-fluoro-4-nitrophenyl)piperazine (15g, 66 6mmol) in DCM (160ml) was cooled to 0°C Triethylamine was then added (11 23ml, 79 92 mmol) followed by dropwise addition of acetyl chloride (5 68ml, 79 92 mmol) The solution was allowed to warm to ambient temperature and stir for 1 5 hour The reaction mixture was diluted with DCM, washed with water, sat. sodium hydrogen carbonate and brine It was dried and the solvent was evaporated to give the title compound as a solid which was dried in vac oven overnight at 50°C (17 46g, 98%) NMR (400MHz) 2 05 (s, 3H), 3 30 (dt, 4H, under H_2O signal), 3 61 (m, 4H), 7 18 (t, 1H), 8 02 (d, 1H), 8 02 (dd, 1H) m/z 268

Method 27

(3*R*,5*S*)-3,5-Dimethyl-1-(4-nitrophenyl)piperazine

1-Fluoro-4-nitrobenzene (10g, 70 87mmol) and (2*R*,6*S*)-2,6-dimethylpiperazine (17g, 148 83mmol) were heated in acetonitrile (25ml) at 70°C for 2h. The solution was concentrated *in vacuo* then the residue was partitioned between DCM and water + sat. sodium hydrogen carbonate. The organic extract was washed with water (4 times), brine, dried and concentrated to give the title compound as a yellow solid which was dried in vac oven overnight at 50°C (16 13g, 97%) NMR (400MHz) 1 04 (d, 6H), 2 39 (m, 2H) 2 77 (m, 2H), 3 89 (dd, 2H), 7 02 (d, 2H), 8 03 (d, 2H), m/z 236

Method 28

(2*S*,5*R*)-2,5-Dimethyl-1-(4-nitrophenyl)piperazine

1-Fluoro-4-nitrobenzene (6g, 42 52mmol) and (2*R*,5*S*)-2,5-dimethylpiperazine (21 9g, 191.34mmol) were heated in acetonitrile (20ml) at 100°C for 11h. The solution was concentrated *in vacuo*, then the residue was partitioned between DCM and water + sat. sodium hydrogen carbonate The organic extract was washed with water (4 times), brine, dried and concentrated. Chromatography on silica gel with MeOH DCM (1 99 to 5 95) gave the title compound as an oil which solidified on standing overnight (8 32g, 83%) NMR (400 MHz) 1 08 (d, 3H), 1 16 (d, 3H), 2 55 (dd, 1H), 3 18 (m, 2H), 3 34 (m, 2H), 3 95 (m, 1H), 6 91 (d, 2H), 8 03 (d, 2H), m/z 236

Method 29

(2*R*,6*S*)-1-Acetyl-2,6-dimethyl-4-(4-nitrophenyl)piperazine

The title compound was prepared from (3*R*,5*S*)-3,5-dimethyl-1-(4-nitrophenyl)piperazine (Method 27 16g, 68 027mmol) and acetyl chloride (8 22ml, 115 65mmol) by the procedure of Method 26 It was obtained as a solid which was dried in vac oven overnight at 50°C (20 5g, 109%, contaminated with solvent) NMR (400MHz) 1 19 (brd, 6H), 2 08 (s, 3H), 3 21 (brd, 2H), 4 00 (d, 2H) 4 34 (v brs, 2H), 7 08 (d, 2H), 8 06 (d, 2H), m/z 278

Method 30

(2*R*,5*S*)-1-Acetyl-2,5-dimethyl-4-(4-nitrophenyl)piperazine

The title compound was prepared from (2*S*,5*R*)-2,5-dimethyl-1-(4-nitrophenyl)piperazine (Method 28, 8 22g, 34 95mmol) and acetyl chloride (4 5ml, 62 91) by the procedure of Method 26 It was obtained as an oil which solidified on standing overnight (11 39g, >100%, contaminated with solvent) NMR (400MHz) 1 13 (m, 6H), 3 07 (m, 1H), 3 33 (m, 1H), 3 68 (m, 1H), 4 25 (m, 2H), 4 69 (m, 1H), 7 00 (d, 2H), 8 05 (d, 2H), m/z 278

Method 31

N-[4-(4-Acetylpiperazin-1-yl)-3-methylphenyl]guanidine bicarbonate salt

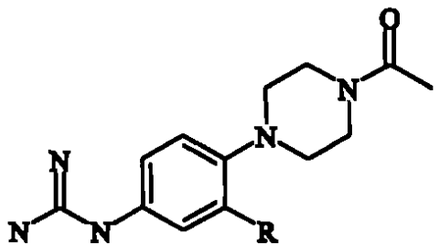
1-Acetyl-4-(2-methyl-4-nitrophenyl)piperazine (Method 25, 19 5g, 74 06 mmol) in EtOH (400 ml) was hydrogenated over 10% Pd / carbon (2 g) at ambient temperature and pressure. The catalyst was filtered off, washed with EtOH (500 ml) and evaporation under reduced pressure to give the aniline as a beige/purple solid which was dried in vac oven overnight at 50°C (17g, 98%)

The aniline (15 5 g, 66 44 mmol) was stirred in dry 1,4-dioxane (120 ml) and EtOH (20 ml) 4N HCl in dioxane (19 93 ml, 79 73 mmol) was then added followed by cyanamide (4 5 g, 106 3mmol) The reaction was heated at 100°C for 2 5 hours under nitrogen, then extra cyanamide (838 mg, 19 93mmol) was added and the reaction was heated for 5 further hours After evaporation under reduced pressure, the solid gum was triturated with ether and solvent re-evaporated. The solid-gum was dissolved in water (small volume), slowly added an excess of saturated sodium hydrogen carbonate solution with stirring After 1 hour, the solid was collected by filtration and dried in vac oven overnight at 60°C to give the title compound. (20 07g, 90%) NMR (400MHz) 2 04 (s, 3H), 2 22 (s, 3H), 2 75 (dt, 4H), 3 30 (brs, 2H, under

H_2O signal), 3 56 (m, 4H), 5 97 (v brs, 3H) 6 66 (dd, 1H), 6 70 (d, 1H), 6 90 (d, 1H), m/z 276

Methods 32-33

The following compounds were prepared by the procedure of Method 31 using the appropriate nitro compound



Meth	R	NMR (400MHz)	m/z	SM
32 [1]	Cl	2 05 (s, 3H), 2 85 (dt, 4H), 3 29 (s, 1H, under H_2O signal), 3 57 (m, 4H), 5 13 (s, 3H), 6 68 (dd, 1H), 6 79 (d, 1H), 6 98 (d, 1H)	296-298	Method 24
33 [2]	F	2 03 (s, 3H), 2 87 (dt, 4H), 3 29 (s, 2H, under H_2O signal), 3 56 (m, 4H), 5 15 (brs, 3H), 6 53 (m, 2H), 6 87 (t, 1H)	280	Method 26

[1] Only 1 4eq cyanamide used, no extra added and only 5 5h heating. Preparation of free base salt dissolved in small amount of water followed by addition of NaOH aq (2 5M) (~22ml) Precipitate formed filtered off to give a dark yellow solid which was dried in vac oven overnight at 50°C (13 34g, 100%)

[2] Extra cyanamide and HCl added and left heating overnight. (14 14g, 68%)

Method 34

N-[4-((3*R*,5*S*)-4-Acetyl 3,5 dimethylpiperazin-1 yl)phenyl]guanidine

The title compound was prepared from (2*R*,6*S*)-1-acetyl-2,6-dimethyl-4-(4-nitrophenyl)piperazine (Method 29, 16 44g, 66 5mmol) and cyanamide (5 03g, 119 7mmol) by the procedure of Method 31 and heating overnight at 95°C The bicarbonate salt was dried in vac oven at 60°C overnight. As it was still wet, it was redissolved in MeOH and acetone and evaporation of solvent gave the title compound as a brown solid (18 6g, 80%) NMR (400MHz) 1 3 (brs, 6H), 2.05 (s, 3H), 2.70 (brd, 2H), 3 35 (m, 4H under H_2O signal), 3 90-4 60 (v brs, 2H), 5 50-6 40 (v brs, 2H), 6 75 (d, 2H), 6 85 (d, 2H), m/z 290

Method 35

N-[4-((2S,5*R*)-4-Acetyl-2,5-dimethylpiperazin-1-yl)phenyl]guanidine

The title compound was prepared from (2*R*,5*S*)-1-acetyl-2,5-dimethyl-4-(4-nitrophenyl)piperazine (Method 30 6 5g, 26 29mmol) and cyanamide (2 43g, 57 84mmol) by the procedure of Method 31 and heating for 10h at 95°C The bicarbonate salt was dried in vac oven at 60°C overnight. It was obtained as a solid (10 23g, >100% contaminated with solvent) M/z 290

Method 36

1 (4-Nitrophenyl)-azetidin-3-ol

A stirred mixture of 4-fluoro-nitrobenzene (12 70g, 90mM), 3 hydroxoyazetidine hydrochloride (10 85g, 99mM) and anhydrous potassium carbonate in acetonitrile (250ml) was heated under reflux for 6hr On cooling, some crystallisation occurred. The reaction mixture was diluted to 1 4l with water and the crystallised material was filtered off, washed with water and dried The title compound was a yellow crystalline solid (14 8g, 85%) NMR. 3 73 (m, 2H), 4 25 (m, 2H), 4 60 (m, 1H), 5 77 (d, 1H), 6 43 (d, 2H), 8 00 (d, 2H), m/z 195

Method 37

1-(4-Aminophenyl)azetidin-3-ol

A stirred solution of 1-(4-nitrophenyl)-azetidin-3-ol (Method 36, 15 15g, 87mM) in EtOH (250ml) was hydrogenated over 10% Pd / C (1 5g) for 18hrs at atmospheric pressure The reaction mixture was filtered and the filtrate was evaporated and triturated with ether giving the title compound as a grey crystalline solid. Much of the product had precipitated from the reaction mixture and been filtered off with catalyst. This was stirred with DMF (100ml) for 15mins and the catalyst filtered off. The filtrate was evaporated (Hi-Vac) and triturated with a little EtOH The second crop of product was filtered off, washed with ether and dried. NMR. 3 35 (m + water, 2H), 3 90 (t, 2H), 4 32 (s, 2H), 4 45 (m, 1H), 5 41 (d, 1H), 6 20 (d, 2H), 6 45 (d, 2H), m/z 165

Method 38

di-*tert*-Butyl ((*E*)-{[4-(3-hydroxyazetidin-1-yl)phenyl]amino}methylylidene)biscarbamate

To a solution of {[(*Z*)-*tert*-butoxycarbonylimino]-trifluoromethanesulfonyl-methyl}-carbamic acid *tert*-butyl ester (13 62g, 34 8mM) and triethylamine (4 9ml, 34 8mM) in dry

DCM (183ml), 1-(4-aminophenyl)azetidin 3-ol (Method 37 6 0g, 36 5mM) was added The solution was stirred at room temperature under nitrogen for 48 hours The reaction mixture was diluted with more DCM and washed with water (twice), saturated sodium bicarbonate solution (twice), water and saturated sodium chloride The solution was then dried with anhydrous sodium sulphate, filtered and evaporated. The crude product was triturated with ether / isohexane (2 1), filtered washed with the same solvent and dried to give the title compound as a yellow solid (11 77g, 83%) NMR 1 4 (s, 9H), 1 5 (s, 9H), 3 47 (t, 1H), 4 02 (t, 2H), 4 5 (m, 1H), 5 55 (d, 1H), 6 38 (d, 2H), 7 23 (d, 2H), 9 75 (s, 1H), 11 46 (m, 1H), m/z 407

Method 39

N-[4-(3-Hydroxyazetidin-1-yl)phenyl]guanidine bicarbonate salt

A solution of di-*tert*-butyl ((*E*)-{[4-(3-hydroxyazetidin 1-yl)phenyl]amino} methylylidene)biscarbamate (Method 38, 250mg, 0 62mM) in TFA (4 5ml) and water (0 52ml) was stirred at room temperature overnight. The water and excess TFA were removed in vacuo The crude salt was dissolved in MeOH (5ml) and macroporous polystyrene carbonate resin (0 49g of capacity 3 0 m.equ per g) solid supported reagent was added and the mixture was gently stirred at room temperature for 4 hours The resin was filtered off and washed with MeOH and the filtrate evaporated to give the title compound as a brown glass (45mg, 77%) NMR 3 47 (t, 2H), 4 05 (t, 2H), 4 54 (m, 1H), 6 42 (d, 2H), 7 0 (d, 2H), m/z 207

Method 40

tert-Butyl [(3*R*)-1-(4-nitrophenyl)pyrrolidin-3-yl]carbamate

tert-Butyl (3*R*)-pyrrolidin-3 ylcarbamate (4 54g, 24 4mmol), 4 fluoronitrobenzene (3 78g, 24 mmol) and potassium carbonate (3 54g 25 6 mmol) in acetonitrile (70ml) were heated under reflux for 18 hours After evaporation under reduced pressure, the mixture was dissolved in DCM (200ml), and washed with water (100ml) and saturated sodium chloride solution (25ml) The solution was dried and filtered. After evaporation under reduced pressure, chromatography on silica gel eluting with with DCM gave the title compound (7 19g, 97%) NMR. 1.39 (s, 9H), 1 87 – 1 98 (m, 1H), 2 09 – 2 21 (m, 1H), 3 15 – 3 23 (m, 1H), 3 32 – 3 44 (m, 1H), 3 45 – 3 51 (m, 1H), 3 53 – 3 61 (m, 1H), 4 09 – 4 21 (m, 1H), 6 57 (d, 2H), 7 21 (s, 1H), 8 01 (d, 2H), m/z (MH^+-C_4H_8) 252

Method 41

(3*R*)-1-(4-Nitrophenyl)pyrrolidin-3-amine trifluoroacetate salt

tert Butyl [(3*R*)-1-(4-nitrophenyl)pyrrolidin-3-yl]carbamate (Method 40, 1 0g, 3 26 mmol) in DCM (15ml) was reacted with TFA (7 5 ml) at room temperature for 18 hours Pouring into cold ether (200ml) gave on filtration the title compound (0 97g, 93%) NMR. 2 03 – 2 17 (m, 1H), 2 22 - 2 44 (m, 1H), 3 40 – 3 60 (m, 3H), 3 68 – 3 74 (m, 1H), 3 95 – 4 08 (m, 1H), 6 66 (d, 2H), 8 08 (d, 2H), 8 14 (s, 2H)

Method 42

N-[(3*R*)-1-(4-Nitrophenyl)pyrrolidin-3 yl]acetamide

(3*R*)-1-(4-Nitrophenyl)pyrrolidin-3-amine trifluoroacetate salt (Method 41, 0 96g, 3mmol) and sodium acetate (0.245g, 3 mmol) in acetic acid (10ml) were reacted with acetic anhydride (0 57 ml, 6 mmol) for 18 hours at room temperature After filtration and washing with ether gave the title compound as a yellow solid (0 63g, 84%) NMR. 1 79 (s, 3H), 1 85 – 1 98 (m, 1H), 2 09 – 2 23 (m, 1H), 3 19 – 3 30 (m, 1H), 3 39 – 3 52 (m, 2H), 3 55 – 3 67 (m, 1H), 4 30 – 4 43 (m, 1H), 6 60 (d, 2H), 8 04 (d, 2H), 8 15 (d, 1H), m/z 250

Method 43

N-[(3*R*)-1-(4-Aminophenyl)pyrrolidin-3-yl]acetamide mono hydrochloride

N-[(3*R*)-1-(4-nitrophenyl)pyrrolidin-3 yl]acetamide (Method 42, 4 5g, 18 mmol) hydrogenated over 10% palladium/carbon at room temperature and 1 atmosphere pressure in absolute alcohol (200ml) After filtration of the catalyst and evaporation at reduced pressure gave *N*-[(3*R*) 1-(4-aminophenyl)pyrrolidin-3-yl]acetamide as a red oil (3 75g, 95%) NMR ($CDCl_3$) 1 97 (s, 3H), 1 89 – 2 03 (m, 1H), 2 22 – 2 34 (m, 1H), 2 54 (s, 2H), 3 06 – 3 27 (m, 2H), 3 34 – 3 48 (m, 2H), 4 52 – 4 68 (m, 1H), 5 79 (brs, 1H), 6 48 (d, 2H), 6 69 (d, 2H), m/z 220 Treatment with 4M hydrogen chloride in 1,4 dioxane gave the title compound (4.21g, 96%) LCMS m/z 220

Method 44

di *tert*-Butyl [(*E*)-({4-[(3*R*)-3-(acetylamino)pyrrolidin-1-yl]phenyl}amino)methylylidene] biscarbamate

N-[(3*R*)-1-(4-aminophenyl)pyrrolidin-3 yl]acetamide mono hydrochloride (Method 43, 2 47g, 9 67 mmol) and Hunigs base (2 02ml, 1 16 mmol) were reacted with di-*tert* butyl

[(*Z*)-1*H*-pyrazol-1-ylmethylylidene]biscarbamate (2 95g, 9 5 mmol) in THF (30ml) at room temperature for 72 hours. After evaporation under reduced pressure, chromatography on silica gel with EtOAc/isohexane (50 50 to 100) gave the title compound as a yellow oil (3 06g, 69%) NMR 1 39 (s, 9H), 1 52 (s, 9H), 1 81 (s, 3H) 1 82 1 93 (m, 1H), 2 11 2 24 (m, 1H) 3 00 – 3 08 (m, 1H), 3 21 – 3 51 (m, 3H), 4 29 – 4 40 (m, 1H), 6 50 (d, 2H), 7 29 (d, 2H), 8 12 (d, 1H), 9 74 (s, 1H), 11 49 (s, 1H), m/z 462

Method 45

4-((3*R*)-Acetamidopyrrolidin-1 yl) phenyl guanidine carbonate

[(*E*)-({4-[(3*R*)-3-(acetylamino)pyrrolidin-1-yl]phenyl}amino)methylylidene] biscarbamate (Method 44 3 06g, 6 6 mmol), was reacted with TFA (20ml) in DCM (100ml) at room temperature under nitrogen for 18 hours. After evaporation under reduced pressure, the residue was dissolved in MeOH (40ml) and treated with macroporous polystyrene carbonate resin (0 49g of capacity 3 0 m.equ per g) (6g), and was stirred for 4 hours The mixture was filtered and washed with MeOH Evaporation under reduced pressure gave the title compound as a grey solid (1.25g, 65%) NMR. 1 80 – 1 94 (m, 1H), 1 83 (s, 3H), 2 09 – 2 22 (m, 1H), 2 96 – 3 09 (m, 1H), 3 19 – 3 29 (m, 1H), 3 30 – 3 39 (m, 1H), 3 40 – 3 52 (m, 1H), 4 28 – 4 41 (m, 1H), 6 52 (d, 2H), 6 91 (d, 2H), 7 32 (brs, 4H), 8 13 (d, 1H), m/z 262

Method 46

tert-Butyl [(3*S*)-1-(4-nitrophenyl)pyrrolidin-3-yl]carbamate

The title compound was prepared by the procedure of Method 40 starting from *tert*-butyl (3*S*)-pyrrolidin 3-ylcarbamate (6 11g, 74%) NMR. 1 36 (s, 9H), 1 83 – 1 98 (m, 1H), 2 08 – 2 20 (m, 1H), 3 12 – 3 24 (m, 1H) 3 31 – 3 51 (m, 2H), 3 52 – 3 65 (m, 1H), 4 09 – 4 23 (m, 1H), 6 58 (d, 2H), 7.20 (s, 1H), 8 01 (d, 2H), m/z 198 (MH^+ C_4H_8)

Method 47

(3*S*)-1-(4-Nitrophenyl)pyrrolidin-3-amine trifluoroacetate salt

The title compound was prepared by the procedure of Method 41 starting from tert-butyl [(3S)-1-(4-nitrophenyl)pyrrolidin-3-yl]carbamate (Method 46) (6 6g, 100%) NMR. 2 03 – 2 19 (m, 1H), 2.20 – 2 40 (m, 1H), 3 25 – 3 75 (m, 3H) 3 94 – 4 04 (m, 1H), 4 38 (brs, 2H), 6 64 (d, 2H), 8 08 (d, 2H), 8 24 (s, 3H) m/z 208

HF 113

Method 48

N [(3*S*)-1-(4-Nitrophenyl)pyrrolidin 3-yl]acetamide

The title compound was prepared by the procedure of Method 42 starting from (3*S*)-1-(4-nitrophenyl)pyrrolidin-3-amine trifluoroacetate salt (Method 47) (4.2g, 93%) NMR 1 80 (s, 3H), 1 86 – 1 98 (m, 1H), 2 11 – 2 24 (m, 1H), 3 15 – 3 28 (m, 1H), 3 37 – 3 55 (m, 2H), 3 64 – 3 70 (m, 1H), 4 32 – 4 44 (m, 1H), 6 61 (d, 2H), 8 04 (d, 2H), 8 15 (d, 1H) m/z 250

Method 49

N-[(3*S*)-1-(4-Aminophenyl)pyrrolidin-3-yl]acetamide

The title compound was prepared by the procedure of Method 43 starting from *N*-[(3*S*)-1-(4-nitrophenyl)pyrrolidin 3-yl]acetamide (Method 48) NMR. 1 79 (s, 3H), 1 69 – 1 88 (m, 1H), 2 07 – 2 20 (m, 1H), 2 82 – 2 93 (m, 1H), 3 01 – 3 14 (m, 1H), 3 16 – 3 38 (m, 2H), 4 25 – 4 36 (m, 1H), 6 31 (d, 2H), 6 51 (d, 2H), 8 08 (d, 1H) + EtOH

Method 50

di-*tert*-Butyl [(*E*)-({4-[(3*R*)-3-(acetylamino)pyrrolidin-1-yl]phenyl}amino)methylylidene] biscarbamate

The title compound was prepared by the procedure of Method 44 starting from *N*-[(3*S*)-1-(4-aminophenyl)pyrrolidin-3-yl]acetamide (Method 49) (4 16g, 45%) NMR 1 31 – 1 56 (brs, 18H), 1 80 (s, 3H), 1 82 – 1 93 (m, 1H), 2.07 – 2 21 (m, 1H), 3 00 – 3 08 (m, 1H), 3 19 – 3 40 (m, 2H), 3 43 – 3 49 (m, 1H), 4 30 – 4 41 (m, 1H), 6 50 (d, 2H), 7 26 (d, 2H), 7 57 (s, 2H), 8 10 (d, 1H), m/z 462

Method 51

4-(3*S*)-Acetamidopyrrolidin-1-yl) phenyl guanidine carbonate

The title compound was prepared by the procedure of Method 45 starting from di-*tert*-butyl [(*E*)-({4-[(3*R*)-3-(acetylamino)pyrrolidin 1-yl]phenyl}amino)methylylidene] biscarbamate (Method 50) (2 26g, 86%) NMR. 1 79 (s, 3H), 1 79 – 1 89 (m, 1H), 2 09 – 2 21 (m, 1H), 2 97 – 3 02 (m, 1H), 3 16 – 3 23 (m, 1H), 3 27 – 3 44 (m, 3H), 4 26 – 4 37 (m, 1H), 6 20 – 6 25 (m, 1H), 6 46 (d, 2H), 6 79 (d, 2H), 7 57 (d, 2H), 8 09 (d, 1H), m/z 262

#6 114

Method 52

(R)-1-(4-Nitro-phenyl)-pyrrolidine-2-carboxylic acid dimethylamide

4-Fluoronitrobenzene (0 47 g, 3 34 mmol), potassium carbonate (1 39, 10 mmol) and (R)-pyrrolidine-2-carboxylic acid dimethylamide (0 50, 3 52mmol) were pre-mixed in acetonitrile (40 ml) and heated at reflux for 36 hours. The reaction was quenched with saturated ammonium chloride (40 ml), extracted with DCM (2 x 100 ml), dried and solvent removed *in vacuo* to yield the title compound as a yellow solid. Ether was added and the solid was stirred, filtered and dried (0 85g, 96%) M/z 264

Method 53

(S)-1-(4-Amino-phenyl)-pyrrolidine-2-carboxylic acid dimethylamide

(R)-1-(4-Nitro-phenyl)-pyrrolidine-2-carboxylic acid dimethylamide (Method 52, 0 85g) was dissolved in MeOH (50 ml), to this was added ammonium formate (1 0 g, 16 mmol) and palladium (0 1 g) The reaction was heated at reflux for 60 minutes (reaction decolourised) MeOH was removed *in vacuo* and saturated ammonium chloride (50 ml) was added. The system was extracted with DCM (2 x100 ml), dried and solvent was removed *in vacuo* to yield the title compound as a brown gum (0 67g, 87%) The product rapidly turned black on exposure to air The product was used immediately without any purification.

Method 54

(S)-1-(4-Guanidino-phenyl)-pyrrolidine-2-carboxylic acid dimethylamide

To *(S)*-1-(4-Amino-phenyl)-pyrrolidine-2-carboxylic acid dimethylamide (Method 53, 0 67g) was added acetonitrile (20 ml) and EtOH (2 ml) HCl in dioxane (0 86 ml, 3 48 mmol) was added and the reaction was stirred for 10 minutes, HCl salt precipitated. Cyanamide (0 2g, 4 9 mmol) was added and the reaction was heated at reflux over the weekend. The black reaction was filtered and the black HCl salt was dissolved in water (5 ml) and basified with $NaHCO_3$ (20 ml) solution No solid was observed, the aqueous was further basified to pH14 with KOH, extracted with DCM (2 x 100 ml), dried and solvent removed *in vacuo* to yield the title compound as a black gum (0 50g, 63%) M/z 276

115

Method 55

(*R*)-1-(4-Nitro-phenyl)-pyrrolidine-2-carboxylic acid

Proline (3 5g, 30 4 mmol), 4-iodonitrobenzene (7.2g, 28 9 mmol), $Pd(PPh_3)_4$ (1 7g, 5mol%), copper iodide (0 3g, 5mol%), benzyltriethylammonium chloride (11 9g, 52mmol), triethylamine (8 3ml, 60 mmol) and potassium carbonate (4 2g, 30 mmol) were pre-mixed in DMF (60 ml)/water (6ml) The reaction was heated at 80°C for 8 hours The DMF was removed *in vacuo* and the remaining black gum was dissolved in DCM, acidified with 2 0 N HCl (50 ml), extracted with DCM (3 x 100 ml), dried and solvent removed *in vacuo* to yield a black tar The tar was dissolved in a minimum amount of DCM (7 ml) and loaded onto a 50 g silica column, the system was eluted with 20%EtOAc/isohexane, then 60%EtOAc/iso-hexnae and finally 100%EtOAc The title compound was obtained as an orange gum. NMR (299 954 MHz, $CDCl_3$) 8 13 (d, 2H), 6 52 (d, 2H), 4 41 (d, 1H), 3 66 (t, 1H), 3 49 (q, 1H), 2 47 - 2 29 (m, 2H), 2.25 - 2 12 (m, 2H), m/z 237

Method 56

(*R*)-1-(4-Nitro-phenyl)-pyrrolidine-2-carboxylic acid methylamide

To (*R*) 1-(4-Nitro-phenyl)-pyrrolidine-2-carboxylic acid (Method 55, 1 8g, 7 6 mmol) in DCM (50 ml) was added HATU (3 2g, 8 4 mmol) and DIPEA (2 0ml, 11 4 mmol) The reaction was stirred for 10 minutes before the addition of methylamine (2 0N in THF, 5 0ml, 15 mmol), the reaction was stirred for 1 hour before being quenched with water (50ml) The reaction was extracted with DCM (3 x 100 ml), dried and solvent removed in *vacuo* to yield a yellow gum Purification was achieved *via* column chromatography eluting with 20%EtOAc/isohexane, 60%EtOAc/isohexane and finally 100%EtOAc The title compound was obtained as an orange gum, (1 4g, 74%) NMR (299 954 MHz, $CDCl_3$) 8 10 (d, 2H), 6 56 (d, 2H), 6 24 (s, 1H), 4 20 (t, 1H), 3 75 (t, 1H), 3 40 (q, 1H), 2 80 (d, 3H), 2 36 2 29 (m, 2H), 2 13 - 2 05 (m, 2H), m/z 250

Method 57

(*R*)-1-(4-Amino-phenyl)-pyrrolidine-2-carboxylic acid methylamide

(*R*)-1 (4-Nitro-phenyl)-pyrrolidine-2-carboxylic acid methylamide (Method 56, 1 2g, 4 8 mmol) was dissolved in MeOH (50 ml), to this was added ammonium formate (1 5 g, 24 mmol) and palladium (0 1 g) The reaction was heated at reflux for 60 minutes, reaction decolourised. MeOH was removed *in vacuo* and saturated ammonium chloride (50 ml) was

added, the system was extracted with DCM (2 x100 ml), dried and solvent removed *in vacuo* to yield the title compound as a brown gum (1 0g, 95%) Product rapidly turned black on exposure to air The product was used immediately without any purification

Method 58

1-[4-({(*E*)-[(*tert*-Butoxycarbonyl)amino][(*tert*-butoxycarbonyl)imino]methyl}amino)phenyl]-*N*-methyl-D-prolinamide

To (*R*)-1-(4-amino-phenyl)-pyrrolidine-2-carboxylic acid methylamide (Method 57 1 0g, 4 5mmol) in DCM (60 ml) was added di-*tert*-butyl [(*Z*)-1*H*-pyrazol 1-ylmethylylidene]biscarbamate (1 7g, 5 5 mmol) in one portion. The reaction was stirred overnight before removal of the solvent *in vacuo* The residue was purified *via* column chromatography eluting with 20%EtOAc/isohexane, 50%EtOAc/iso-hexne and finally 100%EtOAc The title compound was obtained as a white foam (1 9g, 91%)

Method 59

(*R*)-1-(4-Guanidino-phenyl)-pyrrolidine-2-carboxylic acid methylamide

To 1 [4-({(*E*)-[(*tert*-butoxycarbonyl)amino][(*tert* butoxycarbonyl)imino]methyl} amino)phenyl]-*N*-methyl D prolinamide (Method 58, 1 9 g) was added DCM (60 ml) and TFA (20 ml) The reaction was stirred for 4 hours before removal of the solvent *in vacuo* The reaction was basified with 2 0N KOH (20 ml) and extracted with DCM (2 x 50 ml) Product failed to extract in to DCM, the aqueous was reduced down to 90% of the initial volume and re-extracted with DCM (3 x 200 ml), dried and solvent removed *in vacuo* to yield the title compound as a brown solid (0 84g, 78%) NMR (299 955 MHz) 7 79 (q, 1H), 7 57 (s, 1H), 7 18 (s, 2H), 7 03 (d, 2H), 6 48 (d, 2H), 3 91 (d, 1H), 3 58 - 3 54 (m, 1H) 3 17 (q, 1H), 2 56 (d, 3H), 2 19 - 2 09 (m, 2H), 2 01 1 89 (m, 2H), m/z 261

Method 60

(*R*)-1-(4-Nitro-phenyl)-pyrrolidine-2-carboxylic acid cyclopropylamide

To (*R*)-1-(4-nitro-phenyl)-pyrrolidine-2-carboxylic acid (Method 55, 1 8g, 7 6 mmol) in DCM (50 ml) was added HATU (3 2g, 8 4 mmol) and DIPEA (2 0ml, 11 4 mmol) The reaction was stirred for 10 minutes before the addition of methylamine (0 84g, 15 mmol), the reaction was stirred for 1 hour and then quenched with water (50ml) The reaction was extracted with DCM (3 x 100 ml), dried and solvent removed in *vacuo* to yield a yellow gum

Purification was achieved *via* column chromatography eluting with 20%EtOAc/isohexane, 60%EtOAc/isohexane and finally 100% EtOAc. The title compound was obtained as a yellow solid (1 4g, 74%) NMR (299 954 MHz, $CDCl_3$) δ 8 13 (d, 2H), 6 55 (d, 2H), 6 06 (s, 1H), 4 14 (t, 1H), 3 70 (t, 1H), 3 38 (q, 1H), 2.75 - 2 66 (m, 1H), 2 36 - 2 29 (m, 2H), 2 17 - 1 95 (m, 2H), 0 82 - 0 73 (m, 2H), 0 46 - 0 35 (m, 2H), m/z 276

Method 61

(R)-1 (4-Amino-phenyl) pyrrolidine-2-carboxylic acid cyclopropylamide

(*R*)-1 (4-Nitro-phenyl)-pyrrolidine 2-carboxylic acid cyclopropylamide (Method 60, 142g, 5 1 mmol) was dissolved in MeOH (50 ml), to this was added ammonium formate (1 6 g, 26 mmol) and palladium (0 1 g) The reaction was heated at reflux for 60 minutes, reaction decolourised. MeOH was removed *in vacuo* and saturated ammonium chloride (50 ml) was added, the system was extracted with DCM (2 x100 ml), dried and solvent removed *in vacuo* to yield the title compound as a brown gum (1 20g, 96%) Product rapidly turned black on exposure to air The product was used immediately without any purification, m/z 246

Method 62

1 [4-({(*E*)-[(*tert*-Butoxycarbonyl)amino][(*tert* butoxycarbonyl)imino]methyl}amino)phenyl]-*N*-cyclopropyl-D-prolinamide

(*R*)-1-(4-Amino-phenyl)-pyrrolidine-2-carboxylic acid cyclopropylamide (Method 61, 1.2g, 4 9mmol) in DCM (60 ml) was added di-*tert*-butyl [(*Z*)-1*H*-pyrazol-1-ylmethylylidene]biscarbamate (1 9g, 6 1 mmol) in one portion The reaction was stirred overnight before removal of the solvent *in vacuo* The residue was purified *via* column chromatography eluting with 20%ethylactetate/isohexane, 50%EtOAc/isohexane and finally 100% EtOAc The title compound was obtained as a white foam (2 0g, 81%) NMR (299 954 MHz, $CDCl_3$) 11 63 (s, 1H), 10 09 (s, 1H), 7 60 (s, 1H), 7 40 (d, 2H), 6 45 (m, 3H), 3 92 (t, 1H), 3 59 (t, 1H) 3 19 (q, 1H), 2 69 (m, 1H), 2 29 2 22 (m, 2H), 2 03 - 1 84 (m, 2H), 1 53 (s, 9H), 1 49 (s, 9H), 0 80-0 68 (m, 2H), 0 44-0 32 (m, 2H), m/z 488

Method 63

(*R*)-1-(4-Guanidino-phenyl)-pyrrolidine-2-carboxylic acid cyclopropylamide

To 1-[4-({(*E*)-[(*tert*-butoxycarbonyl)amino][(*tert*-butoxycarbonyl)imino]methyl} amino)phenyl]-*N*-cyclopropyl D-prolinamide (Method 62, 2 0 g) was added DCM (60 ml)

and TFA (20 ml) The reaction stirred for 4 hours before removal of the solvent *in vacuo* To the gum was added DCM (75 ml) and macroporous polystyrene carbonate resin (0 49g of capacity 3 0 m.equ per g) solid supported reagent (20g), the reaction was slowly stirred overnight. The reaction was filtered and the solvent removed *in vacuo* to yield very little product. A white solid was present in the filter cup, this was dissolved in MeOH, the resin was also added to the MeOH, the system was stirred for 10 minutes before being filtered, the solvent was removed *in vacuo* to yield the title compound as a white solid (0 90g, 75%) NMR (299 954 MHz, $CDCl_3$) δ 7 26 (s, 3H), 6 85 (d, 2H), 6 49 (d, 2H), 3 93 (d, 1H), 3 62 - 3 60 (m, 1H), 3 17 (q, 1H), 2 70 - 2 62 (m, 1H), 2 32 2 14 (m, 2H), 2 00 - 1 92 (m, 2H), 0 76 - 0 63 (m, 2H), 0 42 (q, 2H), m/z 287

Method 64

tert-Butyl [(3*R*)-1-(2–fluoro-4-nitrophenyl)pyrrolidin-3-yl]carbamate

The title compound was prepared by an analogous route to Method 40 starting from *tert*-butyl (3*R*)-pyrrolidin-3-ylcarbamate (5 40g, 74%) NMR. 1 36 (s, 9H), 1 81 – 1 94 (m, 1H), 2 02 – 2 16 (m, 1H), 3 30– 3 42 (m, 1H), 3 48 – 3 59 (m, 1H), 3 69 – 3 79 (m, H), 4 02 – 4 17 (m, 1H), 6 72 (t, 1H), 7 18 (brs, 1H), 7 92 (d, 2H), m/z 270 ($MH^+ - C_4H_8$)

Method 65

(3*R*)-1-(2-Fluoro-4-nitrophenyl)pyrrolidin-3-amine trifluoroacetate salt

The title compound was prepared by an analogous route to Method 41 starting from *tert*-butyl [(3*R*)-1-(2–fluoro-4-nitrophenyl)pyrrolidin-3 yl]carbamate (Method 64) (5 12g, 94%) NMR. 2 01 – 2 14 (m, 1H), 2 20 – 2 36 (m, 1H), 3 53 – 4 01 (m, 4H), 6 80 (t, 1H), 7 96 (d, 2H), 8 18 (s, 3H), m/z 226

Method 66

N [(3*R*)-1-(2 Fluoro-4-nitrophenyl)pyrrolidin 3-yl]acetamide

The title compound was prepared by an analogous route to Method 42 starting from (3*R*) 1-(2-fluoro-4-nitrophenyl)pyrrolidin 3-amine trifluoroacetate salt (Method 65) (3 78g, 90%) NMR. 1 80 (s, 3H), 1 85 – 1 94 (m, 1H), 2 05 – 2 19 (m, 1H), 3 32 – 3 42 (m, 1H), 3 51 – 3 71 (m, 2H), 3 73 – 3 82 (m, H), 4 28 – 4 36 (m, 1H), 6 72 (t, 1H), 7 38 – 7 92 (n, 2H), 8 11 (d, 1H), m/z 268

Method 67

N-[(3*R*)-1 (4-Amino–2-fluorophenyl)pyrrolidin-3-yl]acetamide

The title compound was prepared by an analogous route to Method 43 starting from *N*-[(3*R*)-1-(2-fluoro-4-nitrophenyl)pyrrolidin-3-yl]acetamide (Method 66) (2 62g, 76%) NMR. 1 64 - 1 76 (m, 1H), 1 79 (s, 3H), 2 02 – 2 16 (m, 1H), 2 87 – 2 92 (m, H), 2 99 – 3 05 (m, 1H), 3 16 – 3 32 (m, 2H), 4 16 – 4 28 (m, 1H), 4 68 (brs, 2H), 6.22 – 6 33 (m, 1H), 6 35 (d, 2H), 6 73 (d, 1H), 8 02 (d, H), m/z 238

Method 68

di-*tert*-Butyl [(*E*)-({2–fluoro-4-[(3*R*)-3-(acetylamino)pyrrolidin-1-yl]phenyl}amino) methylylidene]biscarbamate

The title compound was prepared by an analogous route to Method 44 starting from *N*-[(3*R*)-1-(4-amino–2 fluorophenyl)pyrrolidin-3-yl]acetamide (Method 67) NMR. 1 39 (brs, 9H), 1 46 (brs, 9H), 1 79 (s, 3H) 1 70 – 1 87 (m, 1H), 2 02 – 2 16 (m, 1H), 3 09 – 3 16 (m, 1H), 3 22 – 3 34 (m, 1H), 3 38 – 3 47 (m, 1H), 3 51 – 3 56 (m, 1H), 4 25 – 4 32 (m, 1H), 6 68 (t, 1H), 7 08 (d, 1H), 7 41 (d, 1H), 8 08 (d, 1H), 8 89 (brs, 1H), 9 83 (brs, 1H), 11 41 (brs, 1H), m/z 480

Method 69

2–Fluoro-4-((3R)-acetamidopyrrolidin-1 yl) phenyl guanidine carbonate

The title compound was prepared by an analogous route to Method 45 starting from di-*tert*-butyl [(*E*)-({2–fluoro-4-[(3*R*)-3-(acetylamino)pyrrolidin-1-yl]phenyl}amino) methylylidene]biscarbamate (Method 68) (2 43g, 86%) NMR. 1 75 – 1 86 (m, 1H), 1 80 (s, 3H), 2 06 – 2 18 (m, 1H), 3 21 – 3 38 (m, 2H), 3 50 – 3 60 (m, 1H), 4 21 – 4 34 (m, 1H), 6 72 (t, 1H), 6 89 (d, 1H), 7 00 (d, 1H) 7 29 (brs, 3H), 8 08 (d, 1H), 9 50 (s, 1H)

Method 70

4-((3*R*)-Acetamidopyrrolidin-1 yl) phenyl guanidine trifluoroacetate salt

N-[(3*R*)-1-(4-aminophenyl)pyrrolidin-3-yl]acetamide mono hydrochloride (Method 44, 3 31g, 15 mmol), di *tert*-butyl [(*Z*)-1*H*-pyrazol-1-ylmethylylidene]biscarbamate (5 91g, 15 mmol) and triethylamine (4 17 ml, 30 mmol) in DCM (50 ml) were heated at 40°C for 18 hours After evaporation under reduced pressure, chromatography on silica gel with ethyl acetate/isohexane (50 50 to 100) gave di-*tert* butyl [(*E*)-({ 4-[(3*R*)-3-(acetylamino)pyrrolidin-

1-yl]phenyl}amino)methylylidene] biscarbamate, which was dissolved in DCM (80ml) and treated with TFA (15 ml) at ambient temperature for 18 hours under nitrogen. After evaporation under reduced pressure, the residue was dissolved in MeOH (20ml) and diluted with ether. The title compound was collected by filtration as an off white solid (1.79g, 30% over two steps). NMR. 1.80 (s, 3H), 1.81 – 1.93 (m, 1H), 2.10 – 2.27 (m, 1H), 2.99 – 3.06 (m, 1H), 3.19 – 3.51 (m, 3H), 4.27 – 4.39 (m, 1H), 6.52 (d, 2H), 7.03 (d, 2H), 7.16 (s, 3H), 8.10 (d, 1H) 9.36 (s, 1H).

Example 164

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof (hereafter compound X), for therapeutic or prophylactic use in humans.

(a) Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

(b) Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

(c) Tablet III	mg/tablet
Compound X	1 0
Lactose Ph.Eur	93 25
Croscarmellose sodium	4 0
Maize starch paste (5% w/v paste)	0 75
Magnesium stearate	1 0

(d) Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur	488 5
Magnesium stearate	1 5

(e) Injection I	(50 mg/ml)
Compound X	5 0% w/v
1M Sodium hydroxide solution	15 0% v/v
0 1M Hydrochloric acid	(to adjust pH to 7 6)
Polyethylene glycol 400	4 5% w/v
Water for injection	to 100%

(f) Injection II	10 mg/ml
Compound X	1 0% w/v
Sodium phosphate BP	3 6% w/v
0 1M Sodium hydroxide solution	15 0% v/v
Water for injection	to 100%

5

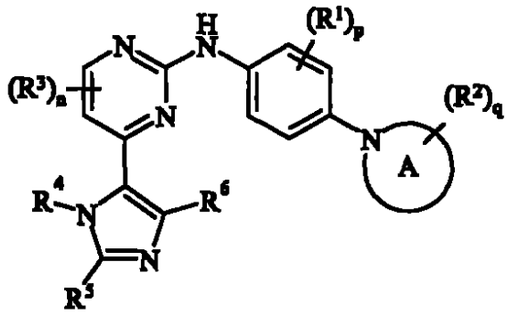
(g) Injection III	(1mg/ml,buffered to pH6)
Compound X	0 1% w/v
Sodium phosphate BP	2 26% w/v
Citric acid	0 38% w/v
Polyethylene glycol 400	3 5% w/v
Water for injection	to 100%

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate

Claims

1 A compound of formula (I)



(I)

wherein

Ring A is a nitrogen linked 4-7 membered saturated ring which optionally contains an additional nitrogen, oxygen or sulphur atom, wherein if Ring A contains an additional nitrogen atom that nitrogen may be optionally substituted by R^7,

R^1 is halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, C_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyl or C_{2-6}alkynyl,

p is 0-4, wherein the values of R^1 may be the same or different,

R^2 is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, azido, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkanoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, carbocyclyl-R^{34}-, heterocyclyl R^{35}-, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl or *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, wherein R^2 independently may be optionally substituted on carbon by one or more R^8, or R^2 is -NHR^9, -NR^{10}R^{11} or -O-R^{12},

q is 0-2, wherein the values of R^2 maybe the same or different;

R^3 is halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-3}alkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{1-3}alkoxy, C_{1-3}alkanoyl, *N*-(C_{1-3}alkyl)amino, *N,N*-(C_{1-3}alkyl)$_2$amino, C_{1-3}alkanoylamino, *N*-(C_{1-3}alkyl)carbamoyl, *N,N*-(C_{1-3}alkyl)$_2$carbamoyl, C_{1-3}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-3}alkyl)sulphamoyl or *N,N*-(C_{1-3}alkyl)$_2$sulphamoyl, wherein R^3 may be independently optionally substituted on carbon by one or more R^{13},

n is 0 to 2, wherein the values of R^3 may be the same or different,

R^4 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carbocyclyl or a carbon-linked heterocyclyl, wherein R^4 may be optionally substituted on carbon by one or more R^{14}, and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{15}

R^5 and R^6 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{3-8}cycloalkyl or a 4-7 membered saturated heterocyclic group wherein R^5 and R^6 independently of each other may be optionally substituted on carbon by one or more R^{16}, and wherein if a 4-7 membered saturated heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17},

R^7, R^9, R^{10}, R^{11} and R^{12} are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{2-6}alkenylsulphonyl, C_{2-6}alkynylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, carbocyclyl, heterocyclyl, carbocyclyl-R^{18}- or heterocyclyl-R^{19}-, wherein R^7, R^9, R^{10}, R^{11} and R^{12} may be independently optionally substituted on carbon by a group selected from R^{20}, and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by R^{21},

R^{14} and R^{20} are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxyC_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC_{1-6}alkyl R^{22} , heterocyclylC_{1-6}alkyl R^{23}-, carbocyclyl-R^{24}- or heterocyclyl R^{25}-, wherein R^{14} and R^{20} may be independently optionally substituted on carbon by one or more R^{26}, and wherein if said heterocyclyl contains an -NH moiety that nitrogen may be optionally substituted by a group selected from R^{27},

R^{18}, R^{19}, R^{22}, R^{23}, R^{24}, R^{25}, R^{34} or R^{35} are independently selected from -O-, -N(R^{28})-, -C(O) , -N(R^{29})C(O)-, -C(O)N(R^{30})-, -S(O)$_s$-, -SO_2N(R^{31})- or -N(R^{32})SO_2-, wherein R^{28} R^{29}, R^{30}, R^{31} and R^{32} are independently selected from hydrogen or C_{1-6}alkyl and s is 0-2

R^{15}, R^{17}, R^{21} and R^{27} and are independently selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl, wherein R^{15}, R^{17}, R^{21} and R^{27} independently of each other may be optionally substituted on carbon by on or more R^{33}, and

R^{8}, R^{13}, R^{16}, R^{26} and R^{33} are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N N*-dimethylcarbamoyl, *N N*-diethylcarbamoyl, *N* methyl *N*-ethylcarbamoyl, methylthio, ethylthio methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl,

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

2 A compound of formula (I) as claimed in claim 1 wherein

Ring A is a nitrogen linked 4-7 membered saturated ring which optionally contains an additional nitrogen or oxygen atom, wherein if Ring A contains an additional nitrogen atom that nitrogen may be optionally substituted by R^7, wherein

R^7 is selected from C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{2-6}alkenylsulphonyl, carbocyclyl R^{18}- or heterocyclyl-R^{19}-, wherein R^7 may be independently optionally substituted on carbon by a group selected from R^{20}, and wherein if said heterocyclyl contains an -NH moiety that nitrogen may be optionally substituted by R^{21},

R^{18} and R^{19} are -C(O)-,

R^{20} is selected from halo, cyano, hydroxy, C_{1-6}alkoxy, C_{2-6}alkynyloxy, C_{1-6}alkanoyloxy, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkylS(O)$_a$ wherein a is 2 or heterocyclyl, wherein R^{20} may be optionally substituted on carbon by one or more R^{26},

R^{21} is C_{1-6}alkyl, and

R^{26} is hydroxy,

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

3 A compound of formula (I) as claimed in either claim 1 or claim 2 wherein R^1 is halo or C_{1-6}alkyl or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

4 A compound pf formula (I) as claimed in any one of claims 1-3 wherein p is 0 or 1 or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

5 A compound pf formula (I) as claimed in any one of claims 1-4 wherein

R^2 is selected from hydroxy, amino, azido, C_{1-6}alkyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, carbocyclyl R^{34}-, NHR^9 or -O R^{12},

R^9 and R^{12} are independently selected from C_{1-6}alkanoyl or C_{1-6}alkylsulphonyl, wherein R^9 and R^{12} may be independently optionally substituted on carbon by a group selected from R^{20},

R^{20} is hydroxy, and

R^{34} is -N(R^{29})C(O)-, wherein R^{29} is hydrogen,

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

6 A compound pf formula (I) as claimed in any one of claims 1-5 wherein R^3 is halo or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

7 A compound pf formula (I) as claimed in any one of claims 1-6 wherein n is 0 or 1 or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

8 A compound pf formula (I) as claimed in any one of claims 1-7 wherein

R^4 is C_{1-6}alkyl or carbocyclyl, wherein R^4 may be optionally substituted on carbon by one or more R^{14}, wherein

R^{14} is carbocyclyl,

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

9 A compound of formula (I) as claimed in any one of claims 1 8 wherein

R^5 and R^6 are independently selected from hydrogen or C_{1-6}alkyl, wherein R^5 and R^6 independently of each other may be optionally substituted on carbon by one or more R^{16}, wherein

R^{16} is selected from methoxy,

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof

A compound of formula (I), as depicted in claim 1, wherein

Ring A, R^2 and q together form piperazin-1 yl, morpholino, 4-mesylpiperazin 1 yl, 4-acetylpiperazin 1-yl 4-(2-acetoxyacetyl)piperazin-1 yl, 4-(2-hydroxyacetyl)piperazin-1-yl, 4-(2-chloroacetyl)piperazin-1-yl, 4-(2-methoxyacetyl)piperazin-1-yl, (3-methoxypropanoyl)piperazin-1-yl, (3-hydroxy-3-methylbutanoyl)piperazin-1-yl, (3-hydroxy 2,2-dimethylpropanoyl)piperazin 1-yl, ((R)-3-methyl-2-hydroxybutanoyl)piperazin-1-yl, ((S)-3-methyl-2-hydroxybutanoyl)piperazin-1-yl, 4-(2-dimethylaminoacetyl)piperazin-1-yl, 4-[2-(dimethylamino)ethylsulphonyl]piperazin 1-yl, 4-[2-(methoxy)ethylsulphonyl]piperazin-1 yl, 4-[2-(hydroxy)ethylsulphonyl]piperazin-1-yl, 4-(cyclopropylcarbonyl)piperazin 1-yl, 4-(1-hydroxycyclopropylcarbonyl)piperazin-1-yl, 4-(1-cyanocyclopropylcarbonyl)piperazin-1-yl, 4-(2-hydroxy-2-methylpropanoyl)piperazin-1 yl, 4-((R)-2-hydroxypropanoyl)piperazin 1-yl, 4-((S)-2-hydroxypropanoyl)piperazin-1-yl, 4-((R)-2 methoxypropanoyl)piperazin-1-yl, 4-((S)-2-methoxypropanoyl)piperazin-1-yl 4-((R)-tetrahydrofuran-2-ylcarbonyl)piperazin-1-yl, 4-((S)-tetrahydrofuran-2-ylcarbonyl)piperazin 1-yl, 4-(isobutyryl)piperazin-1-yl, 4-((R)-2 hydroxybutanoyl)piperazin-1-yl, 4-((S)-2 hydroxybutanoyl)piperazin-1 yl, (R)-3-acetylaminopyrrolidin-1-yl, (S)-3-acetylaminopyrrolidin-1-yl, (R)-2-(cyclopropylaminocarbonyl)pyrrolidin 1 yl, (R)-2-(*N*-methylcarbamoyl)pyrrolidin-1 yl, (S)-2-(*N N*-dimethylcarbamoyl)pyrrolidin-1 yl, 4-(ethenylsulphonyl)piperazin-1-yl, 4-[2-(2 propyn-1-yloxy)acetyl]piperazin 1-yl, 4-(tetrahydrofuran-3-ylcarbonyl)piperazin-1 yl, 4-(3 dimethylaminopropanoyl)piperazin-1 yl, 4-[2-(*N*-methyl-*N*-hydroxymethylamino)acetyl]piperazin-1 yl, 4-[3-hydroxy-2 (hydroxymethyl)propanoyl]piperazin 1 yl, 4-[2-(1,2,3,4-tetrazol-1-yl)acetyl]piperazin 1-yl, 4-[2-(1,2,3,4-tetrazol-5-yl)acetyl]piperazin-1-yl, 4-(1-methyl-L-prolyl)piperazin-1-yl, 4-[2-(mesyl)acetyl]piperazin-1-yl, 4-(2,2-difluoroacetyl)piperazin-1-yl, 4-[2-(pyrrolidin-1-yl)acetyl]piperazin-1 yl, 4-[2-(morpholino)acetyl]piperazin 1-yl, 4-[2-(diethylamino)acetyl]piperazin-1 yl 4-(propionyl)piperazin 1-yl, 4-(3-hydroxypropionyl)piperazin-1-yl, 4-[2-(azetidin 1-yl)acetyl]piperazin-1-yl, (R)-3-aminopyrrolidin-1-yl, (S)-3-aminopyrrolidin-1-yl, (3*R*,5*S*)-4-acetyl-3,5-dimethylpiperazin-1 yl, (2*S*,5*R*)-4-acetyl-2,5-dimethylpiperazin-1-yl, (2*RS*,6*SR*)-2,6-dimethylmorpholin-4-yl]phenyl, 3 hydroxyazetidin-1-yl, 3-acetylaminoazetidin-1 yl, 3 (2-hydroxyacetylamino)azetidin-1-yl, 3-mesylaminoazetidin-1-yl, 3-mesyloxyazetidin-1-yl, 3-

azidoazetidin-1-yl, 3-aminoazetidin-1-yl, (3*R*)-3-{[(2*S*)-2-hydroxypropanoyl]amino}pyrrolidin-1 yl (3*S*)-3-{[(2*S*)-2-hydroxypropanoyl]amino}pyrrolidin-1-yl, (3*S*) 3-(glycoloylamino)pyrrolidin-1-yl and (3*R*)-3-(glycoloylamino)pyrrolidin-1-yl,

R^1 is fluoro, chloro or methyl,

p is 0 or 1,

R^2 is selected from hydroxy, amino, azido, methyl, *N* methylcarbamoyl, *N N*-dimethylcarbamoyl, acetamido, {[(2*S*)-2-hydroxypropanoyl]amino}, glycoloylamino, mesylamino, 2-hydroxyacetamido, mesyloxy or *N*-cyclopropylcarbamoyl

q is 0-2, wherein the values of R^2 maybe the same or different,

R^3 is 5 fluoro or 5-chloro,

n is 0 or 1,

R^4 is ethyl, isopropyl, isobutyl, cyclobutyl or cyclopropylmethyl,

R^5 and R^6 are independently selected from hydrogen, methyl, ethyl, methoxymethyl, propyl,

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof

11 A compound of formula (I), as depicted in claim 1, selected from

2 {4-[4-(2-hydroxyacetyl)piperazin 1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H* imidazol-5-yl)-5-fluoropyrimidine hydrochloride,

2 {4-[4-(2 hydroxyacetyl)piperazin-1-yl]anilino}-4-(1 isopropyl-2-methyl-1*H* imidazol 5-yl)pyrimidine,

(2*S*)-1-[4-(4-{[5 fluoro-4-(1-isopropyl 2 methyl 1*H*-imidazol 5-yl)pyrimidin-2 yl]amino}phenyl)piperazin-1-yl]-1-oxopropan 2-ol,

2-[4-(morpholino)anilino]-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine

2-{4-[4-(acetyl)piperazin-1-yl]anilino}-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)-5-fluoropyrimidine,

2-[4-(4-acetylpiperazin 1-yl)anilino]-4-(1-isopropyl-2 methyl 1*H*-imidazol 5-yl)pyrimidine,

5-fluoro-4-(1-isopropyl-2-methyl-1*H*-imidazol-5-yl)-*N*-{4-[4-(methoxyacetyl)piperazin-1-yl]phenyl}pyrimidin-2-amine,

N [4-(4-acetylpiperazin 1-yl)-3 fluorophenyl]-5 fluoro-4-(1-isopropyl-2-methyl 1*H*-imidazol-5 yl)pyrimidin-2-amine,

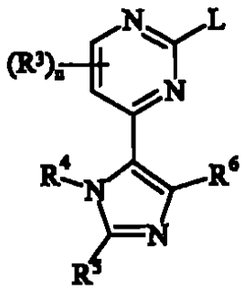
N-[4-(4-acetylpiperazin-1-yl)-3-fluorophenyl]-4-(1 isopropyl-2-methyl-1*H* imidazol-5-yl)pyrimidin-2-amine and

(2*R*)-1-[4-(4-{[5-fluoro-4-(1-isopropyl 2-methyl 1*H* imidazol-5-yl)pyrimidin 2-yl]amino}phenyl)piperazin-1-yl]-1-oxopropan-2-ol,

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

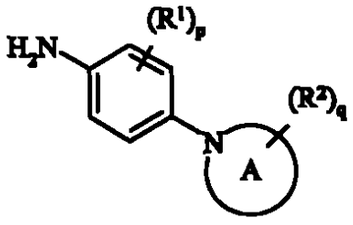
12 A process for preparing a compound of formula (I), as claimed in any one of claims 1-11, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, which process, wherein variable groups are, unless otherwise specified, as defined claim 1, comprises of

Process a) reaction of a pyrimidine of formula (II)



(II)

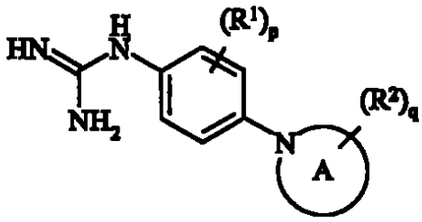
wherein L is a displaceable group, with an aniline of formula (III)



(III)

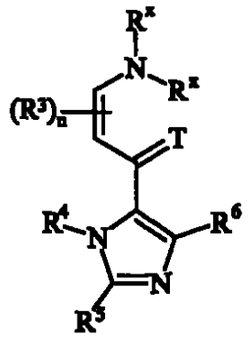
or

Process b) reacting a compound of formula (IV)



(IV)

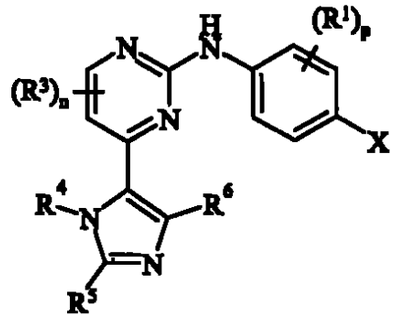
with a compound of formula (V)



(V)

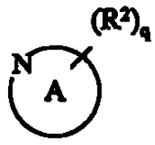
wherein T is O or S, R^x may be the same or different and is selected from C_{1-6}alkyl, or

Process c) reacting a pyrimidine of formula (VI)



(VI)

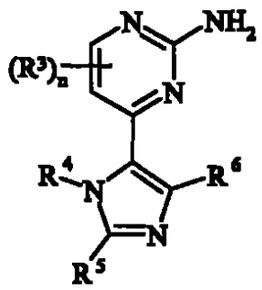
wherein X is a displaceable group, with a heterocyclyl of formula (VII)



(VII)

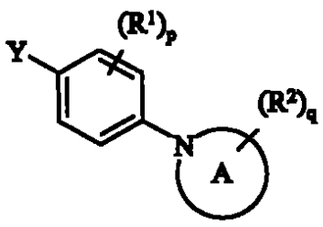
or

Process d) for compounds of formula (I), reacting a pyrimidine of formula (VIII)



(VIII)

with a compound of formula (IX)



(IX)

where Y is a displaceable group,

and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I),

ii) removing any protecting groups,

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester

13 A pharmaceutical composition which comprises a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1 11, in association with a pharmaceutically-acceptable diluent or carrier

14 A compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-11, for use in a method of treatment of the human or animal body by therapy

15 A compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-11, for use as a medicament.

16 The use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-11, in the manufacture of a

medicament for use in the production of a cell cycle inhibitory, anti-cell-proliferation, effect in a warm-blooded animal such as man.

17 The use of a compound of the formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-11 in the manufacture of a medicament for use in the treatment of cancers, solid tumours and leukaemias, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation, particularly in the treatment of cancers.

18 The use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-11, in the manufacture of a medicament for use in the treatment of cancer

19 The use according to claim 18 wherein said cancer is leukaemia, breast cancer, lung cancer, colon cancer, rectal cancer, stomach cancer prostate cancer, bladder cancer cancer of the pancreas, ovarian cancer, liver cancer, kidney cancer, skin cancer and cancer of the vulva

20 The use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1 11, in the manufacture of a medicament for use in the production of a CDK inhibitory effect.

21 A method for producing a cell cycle inhibitory, anti-cell-proliferation, effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), as claimed in any one of claims 1-11

22 A method of treating cancers, solid tumours and leukaemias, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation, in a warm-blooded animal, such as man, in need of such treatment which

comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-11

23 A method of treating cancer in a warm blooded animal such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, as claimed in any one of claims 1-11

24 A method as claimed in claim 23 wherein said cancer is leukaemia, breast cancer, lung cancer, colon cancer, rectal cancer, stomach cancer, prostate cancer, bladder cancer, cancer of the pancreas, ovarian cancer, liver cancer, kidney cancer, skin cancer and cancer of the vulva.

25 A method of producing a CDK inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, as claimed in any one of claims 1-11

26 A pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-11, in association with a pharmaceutically-acceptable diluent or carrier for use in the production of a cell cycle inhibitory, anti-cell-proliferation, effect in a warm-blooded animal such as man.

27 A pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-11, in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of cancers, solid tumours and leukaemias, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation, in a warm-blooded animal such as man.

28 A pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1 11 in association with a pharmaceutically-acceptable diluent or carrier for use in the treatment of cancer in a warm-blooded animal such as man.

29 A pharmaceutical composition as claimed in claim 28 wherein said cancer is leukaemia, breast cancer, lung cancer, colon cancer, rectal cancer, stomach cancer, prostate cancer, bladder cancer, cancer of the pancreas, ovarian cancer, liver cancer, kidney cancer, skin cancer and cancer of the vulva.

30 A pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in any one of claims 1-11, in association with a pharmaceutically-acceptable diluent or carrier for use in the production of a CDK inhibitory effect in a warm-blooded animal such as man

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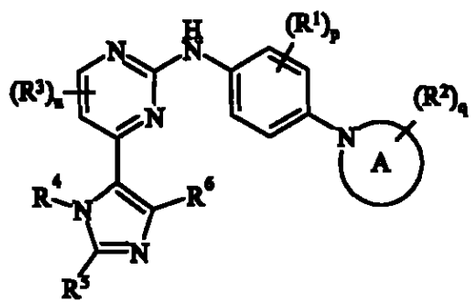
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(54) Título: IMIDAZOLO-5-IL-2-ANILINOPIRIMIDINAS COMO AGENTES PARA LA INHIBICIÓN DE LA PROLIFERACIÓN CELULAR



(57) Extracto: Se describen compuestos de la fórmula (I) en donde grupos variables son como se definen en ella, y sales farmacéuticamente aceptables y ésteres hidrolizables *in vivo*. Se describen igualmente procesos para su preparación y su empleo como medicamentos, particularmente medicamentos para producir un efecto inhibidor del ciclo celular (anti-proliferación celular) en un animal de sangre caliente, tal como el hombre.

WO 2005/075461 A1

COMPUESTOS QUÍMICOS

La invencion concierne a derivados de pirimidina, o sales farmaceuticamente aceptables o sus ésteres hidrolizables *in vivo*, que poseen actividad inhibidora del ciclo celular y, en consecuencia, son utiles por su actividad antiproliferacion celular (tal como antineoplasica) y, por lo tanto, son utiles en métodos de tratamiento del cuerpo humano o animal La invencion se relaciona igualmente con procesos para la fabricación de dichos derivados de pirimidina, con composiciones farmaceuticas que los contienen y con su uso en la fabricación de medicamentos de empleo en la producción de un efecto antiproliferacion celular en un animal de sangre caliente tal como el hombre

El ciclo celular es fundamental para la supervivencia, regulación y proliferación de células y esta altamente regulado para garantizar que cada paso proceda de una manera oportuna y ordenada La progresion de las células a traves del ciclo celular obedece a la activación secuencial y la desactivación de varios miembros de la familia de ciclinas dependientes de cinasa (CDK) La activacion de CDKs depende de su interaccion con una familia de proteinas intracelulares llamadas ciclinas La ciclinas se unen a las CDKs y esta asociacion es esencial para la actividad CDK (tales como CDK1, CDK2, CDK4 y/o CDK6) en la celulas Diferentes ciclinas se expresan y degradan en diferentes puntos en el ciclo celular para garantizar que la activacion e inactivación de CDKs ocurra en el orden correcto de progresión a través del ciclo celular

Mas aun, las CDKs parecen estar corriente abajo de un numero de vias señalizadoras de oncogenes La desregulacion de la actividad CDK mediante la regulación ascendente de ciclinas y/o la eliminacion de inhibidores endogenos parece ser un eje importante entre las vias de señalizacion mitogénicas y la proliferacion de las células neoplasicas

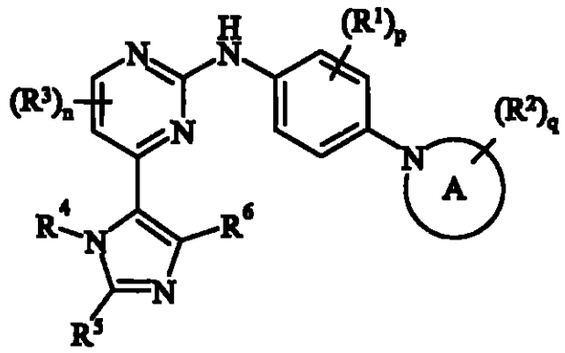
En consecuencia, se ha reconocido que un inhibidor de las cinasas del ciclo celular, particularmente los inhibidores de CDK1, CDK2 y/o CDK4 (que operan en la fase, G2/M, G1/S-S-G2/M y la fase G1-S

respectivamente) debe ser valioso como un activo inhibidor de la proliferacion celular, tal como el crecimiento de celulas cancerosas de mamifero

Se espera que la inhibición de cinasas del ciclo celular sea útil en el tratamiento de estados patologicos asociados con ciclos celulares aberrantes y proliferacion celular tales como neoplasias malignas (tumores sólidos y leucemias), trastornos de fibroproliferacion y diferenciacion, psoriasis, artritis reumatoide, sarcoma de Kaposi, hemangioma, nefropatias agudas y cronicas, ateroma, arteriosclerosis, restenosis arterial, enfermedades autoinmunitarias, inflamación cronica y aguda, enfermedades oseas y afecciones oculares con proliferacion vascular retiniana

WO 02/20512, WO 03/076435, WO 03/076436, WO 03/076434 y WO 03/076433 describen ciertos derivados de 2-anilino-4-imidazolilpirimidina que inhiben el efecto de cinasas del ciclo celular La presente invencion se basa en el descubrimiento de que un grupo novedoso de 2-(4-heterociclilanilino)-4-imidazolilpirimidinas sorprendentemente inhiben los efectos de cinasas del ciclo celular que muestran actividad contra CDK1 y CDK2, particularmente CDK2 y, por lo tanto, poseen propiedades de anti-proliferacion celular Los compuestos de la presente invencion no se divulgan especificamente en alguna de las solicitudes anteriores, y hemos descubierto sorpresivamente que estos compuestos poseen propiedades beneficas en terminos de una o mas de su actividad farmacologica (particularmente como compuestos que inhiben CDK2) y/o perfiles farmacocinéticos, eficaces, metabólicos y toxicológicos que los hacen particularmente apropiados para administracion *in vivo* a un animal de sangre caliente, tal como el hombre En particular estos compuestos muestran propiedades físicas y metabólicas mejoradas, comparados con los divulgados anteriormente

Por consiguiente, la presente invencion provee un compuesto de formula (I)



(I)

en donde

Anillo A es un anillo saturado de 4-7 miembros, enlazado a nitrogeno, que contiene opcionalmente un atomo adicional de nitrogeno, oxigeno o azufre, en donde si Anillo A contiene un atomo adicional de nitrogeno, es nitrogeno puede sustituirse opcionalmente por R^7,

R^1 es halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, C_{1-6}alquilo, C_{1-6}alcoxi, C_{2-6}alquenilo o C_{2-6}alquinilo,

p es 0-4, en donde los valores de R^1 pueden ser los mismos o diferentes,

R^2 se selecciona de halo, nitro, ciano, hidroxi, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, azido, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcanoilo, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$ carbamoilo, carbociclil-R^{34}-, heterociclil-R^{35}-, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, *N*-(C_{1-6}alquil)sulfamoilo o *N*,*N*-(C_{1-6}alquil)$_2$ sulfamoilo, en donde R^2 independientemente puede sustituirse de manera opcional en carbono por uno o más R^8, o R^2 es -NHR^9, -NR^{10}R^{11} o -O-R^{12},

q es 0-2, en donde los valores de R^2 pueden ser los mismos o diferentes,

R^3 es halo, nitro, ciano, hidroxi, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-3}alquilo, C_{2-3}alquenilo, C_{2-3}alquinilo, C_{1-3}alcoxi, C_{1-3}alcanoilo, *N*-(C_{1-3}alquil)amino, *N*,*N*-(C_{1-3}alquil)$_2$amino, C_{1-3}alcanoilamino, *N*-(C_{1-3}alquil)carbamoilo, *N*,*N*-(C_{1-3}alquil)$_2$carbamoilo, C_{1-3}alquilS(O)$_a$ en donde a es 0 a 2, *N*-(C_{1-3}alquil)sulfamoilo o *N*,*N*-(C_{1-3}alquil)$_2$sulfamoilo, en donde R^3 puede

sustituirse independientemente de manera opcional en carbono por uno o mas R^{13},

n es 0 a 2, en donde los valores de R^3 pueden ser los mismos o diferentes,

R^4 es hidrógeno, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, carbociclilo o un heterociclilo enlazado a carbono, en donde R^4 puede sustituirse de manera opcional en carbono por uno o mas R^{14}, y en donde, si dicho heterociclilo contiene una fraccion -NH-, ese nitrogeno puede sustituirse opcionalmente por un grupo seleccionado de R^{15},

R^5 y R^6 se seleccionan independientemente de hidrogeno, halo, nitro, ciano, hidroxi, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino, C_{3-8}cicloalquilo un grupo heterociclico saturado de 4-7 miembros, en donde R^5 y R^6 independientemente uno de otro puede sustituirse de manera opcional en carbono por uno o mas R^{16}, y en donde, si dicho grupo heterociclico saturado de 4-7 miembros contiene una fraccion -NH-, ese nitrogeno puede sustituirse opcionalmente por un grupo seleccionado de R^{17},

R^7, R^9, R^{10}, R^{11} y R^{12} se seleccionan independientemente de C_{1-6}alquilo, C_{1-6}alcanoilo, C_{1-6}alquilsulfonilo, C_{2-6}alquenilsulfonilo, C_{2-6}alquinilsulfonilo, C_{1-6}alcoxicarbonilo, carbamoilo, *N*-(C_{1-6}alquil) carbamoilo, *N,N*-(C_{1-6}alquil)carbamoilo, carbociclilo, heterociclilo, carbociclil-R^{18}- o heterociclil- R^{19}-, en donde R^7, R^9, R^{10}, R^{11} y R^{12} pueden sustituirse independientemente de manera opcional en carbono por un grupo seleccionado de R^{20}, y en donde, si dicho heterociclilo contiene una fracción -NH-, ese nitrogeno puede sustituirse opcionalmente por R^{21},

R^{14} y R^{20} se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{2-6}alqueniloxi, C_{2-6}alquiniloxi, C_{1-6}

$_6$alcoxiC$_{1-6}$alcoxi, C$_{1-6}$alcoxiC$_{1-6}$alcoxiC$_{1-6}$alcoxi, C$_{1-6}$alcanoilo, C$_1$ $_6$alcanoiloxi, *N*-(C$_{1-6}$alquil)amino, *N*,*N*-(C$_{1-6}$alquil)$_2$amino, C$_1$ $_6$alcanoilamino, *N*-(C$_{1-6}$alquil)carbamoilo, *N*,*N*-(C$_{1-6}$alquil)$_2$carbamoilo, C$_1$ $_6$alquilS(O)$_a$ en donde **a** es 0 a 2, C$_{1-6}$alcoxicarbonilo, *N*-(C$_{1-6}$alquil) sulfamoilo, *N*,*N*-(C$_{1-6}$alquil)$_2$sulfamoilo, C$_{1-6}$alquilsulfonilamino, carbociclilo, heterociclilo, carbociclilC$_{1-6}$alquil-R^{22}-, heterociclilC$_{1-6}$alquil-R^{23}-, carbociclil-R^{24}- o heterociclil-R^{25}-, en donde R^{14} y R^{20} pueden sustituirse independientemente de manera opcional en carbono por uno o mas R^{26}, y en donde, si dicho heterociclilo contiene una fraccion -NH-, ese nitrogeno puede sustituirse opcionalmente por un grupo seleccionado de R^{27},

R^{18}, R^{19}, R^{22}, R^{23}, R^{24}, R^{25}, R^{34} o **R^{35}** se seleccionan independientemente de -O-, -N(R^{28})-, -C(O)-, -N(R^{29})C(O)-, -C(O)N(R^{30})-, S(O)$_s$-, -SO$_2$N(R^{31})- o -N(R^{32})SO$_2$-, en donde **R^{28}, R^{29}, R^{30}, R^{31}** y **R^{32}** se seleccionan independientemente de hidrógeno o C$_{1-6}$alquilo y s es 0-2,

R^{15}, R^{17}, R^{21} y **R^{27}** se seleccionan independientemente de C$_{1-6}$alquilo, C$_{1-6}$alcanoilo, C$_{1-6}$alquilsulfonilo, C$_{1-6}$alcoxicarbonilo, carbamoilo, *N*-(C$_1$ $_6$alquil)carbamoilo, *N*,*N*-(C$_{1-6}$alquil)carbamoilo, bencilo, benciloxicarbonilo, benzoilo y fenilsulfonilo, en donde R^{15}, R^{17}, R^{21} y R^{27} independientemente uno de otro pueden sustituirse de manera opcional en carbono por uno o mas R^{33}, y

R^8, R^{13}, R^{16}, R^{26} y **R^{33}** se seleccionan independientemente de halo, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N*,*N*-dimetilcarbamoilo, *N*,*N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N*,*N*-dimetilsulfamoilo, *N*,*N*-dietilsulfamoilo o *N*-metil-*N*-etilsulfamoilo,

o su sal farmacéuticamente aceptable o ester hidrolizable *in vivo*

De acuerdo con un aspecto adicional de la invención se provee un compuesto de formula (I) (como se describe más arriba) en donde

Anillo A es un anillo saturado de 4-7 miembros, enlazado a nitrogeno, que contiene opcionalmente un atomo adicional de nitrogeno, oxigeno o azufre, en donde si Anillo A contiene un atomo adicional de nitrogeno, ese nitrogeno puede sustituirse opcionalmente por R^7,

R^1 es halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, C_{1-6}alquilo, C_{1-6}alcoxi, C_{2-6}alquenilo o C_{2-6}alquinilo,

p es 0-4, en donde los valores de R^1 pueden ser los mismos o diferentes,

R^2 se selecciona de halo, nitro, ciano, hidroxi, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcanoilo, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde **a** es 0 a 2, C_{1-6}alcoxicarbonilo, *N*-(C_{1-6}alquil)sulfamoilo o *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, en donde R^2 independientemente puede sustituirse de manera opcional en carbono por uno o más R^8, o R^2 es -NHR^9, -NR^{10}R^{11} o -O-R^{12},

q es 0-2, en donde los valores de R^2 pueden ser los mismos o diferentes,

R^3 es halo, nitro, ciano, hidroxi, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-3}alquilo, C_{2-3}alquenilo, C_{2-3}alquinilo, C_{1-3}alcoxi, C_{1-3}alcanoilo, *N*-(C_{1-3}alquil)amino, *N,N*-(C_{1-3}alquil)$_2$amino, C_{1-3}alcanoilamino, *N*-(C_{1-3}alquil)carbamoilo, *N,N*-(C_{1-3}alquil)$_2$carbamoilo, C_{1-3}alquilS(O)$_a$ en donde **a** es 0 a 2, *N*-(C_{1-3}alquil)sulfamoilo o *N,N*-(C_{1-3}alquil)$_2$sulfamoilo, en donde R^3 puede sustituirse independientemente de manera opcional en carbono por uno o mas R^{13},

n es 0 a 2, en donde los valores de R^3 pueden ser los mismos o diferentes,

R^4 es hidrogeno, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, carbociclilo o un heterociclilo enlazado a carbono, en donde R^4 puede sustituirse de manera opcional en carbono por uno o mas R^{14}, y en donde si dicho

heterociclilo contiene una fraccion -NH-, ese nitrogeno puede sustituirse opcionalmente por un grupo seleccionado de R^{15},

R^5 y R^6 se seleccionan independientemente de hidrogeno, halo, nitro, ciano, hidroxi, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, *N*-(C_{1-6}alquil)sulfamoilo, *N*,*N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino, C_{3-8}cicloalquilo o un grupo heterocíclico saturado de 4-7 miembros, en donde R^5 y R^6 independientemente uno de otro pueden sustituirse de manera opcional en carbono por uno o más R^{16}, y en donde, si dicho grupo heterociclico saturado de 4-7 miembros contiene una fraccion -NH-, ese nitrogeno puede sustituirse opcionalmente por un grupo seleccionado de R^{17},

R^7, R^9, R^{11}, R^{12} y R^{12} se seleccionan independientemente de C_{1-6}alquilo, C_{1-6}alcanoilo, C_{1-6}alquilsulfonilo, C_{2-6}alquenilsulfonilo, C_{2-6}alquinilsulfonilo, C_{1-6}alcoxicarbonilo, carbamoilo, *N*-(C_{1-6}alquil) carbamoilo, *N*,*N*-(C_{1-6}alquil)carbamoilo, carbociclilo, heterociclilo, carbociclil-R^{18}- o heterociclil-R^{19}-, en donde R^7, R^9, R^{10}, R^{11} y R^{12} pueden sustituirse independientemente de manera opcional en carbono por un grupo seleccionado de R^{20}, y en donde si dicho heterociclilo contiene una fraccion -NH-, ese nitrogeno puede sustituirse opcionalmente por R^{21},

R^{14} y R^{20} se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alcoxiC_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, *N*-(C_{1-6}alquil)sulfamoilo, *N*,*N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino, carbociclilo, heterociclilo, carbociclilC_{1-6}alquil-R^{22}-, heterociclilC_{1-6}alquil-R^{23}-, carbociclil-R^{24}- o heterociclil-R^{25}-, en donde R^{14}

y R^{20} puede sustituirse de manera opcional en carbono por uno o mas R^{26}, y en donde si dicho heterociclilo contiene una fraccion -NH-, ese nitrogeno puede sustituirse opcionalmente por un grupo seleccionado de R^{27},

R^{18}, R^{19}, R^{22}, R^{23}, R^{24}, R^{25} se seleccionan independientemente de -O-, -N(R^{28})-, -C(O)-, -N(R^{29})C(O)-, -C(O)N(R^{30})-, -S(O)$_s$-, -SO_2N(R^{31})- o -N(R^{32})SO_2-, en donde **R^{28}**, **R^{29}**, **R^{30}**, **R^{31}** y **R^{32}** se seleccionan independientemente de hidrógeno o C_{1-6}alquilo y **s** es 0-2,

R^{15}, R^{17}, R^{21} y **R^7** se seleccionan independientemente de C_{1-6}alquilo, C_{1-6}alcanoilo, C_{1-6}alquilsulfonilo, C_{1-6}alcoxicarbonilo, carbamoilo, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)carbamoilo, bencilo, benciloxicarbonilo, benzoilo y fenilsulfonilo, en donde R^{15}, R^{17}, R^{21} y R^{27} independientemente uno de otro pueden sustituirse de manera opcional en carbono por uno o más R^{33}, y

R^8, R^{13}, R^{16}, R^{26} y **R^{33}** se seleccionan independientemente de halo, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N*,*N*-dimetilcarbamoilo, *N*,*N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N*,*N*-dimetilsulfamoilo, *N*,*N*-dietilsulfamoilo o *N*-metil-*N*-etilsulfamoilo,

o su sal farmaceuticamente aceptable o ester hidrolizable *in vivo*

De acuerdo con un aspecto adicional de la invencion se provee un compuesto de formula (I) (como se describe más arriba) en donde

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R^1 es halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, C_{1-6}alquilo, C_{1-6}alcoxi, C_{2-6}alquenilo o C_{2-6}alquinilo,

p es 0-4, en donde los valores de R^1 pueden ser los mismos o diferentes,

R^2 se selecciona de halo, nitro, ciano, hidroxi, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcanoilo, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, *N*-(C_{1-6}alquil)sulfamoilo o *N*,*N*-(C_{1-6}alquil)$_2$sulfamoilo, en donde R^2 independientemente puede sustituirse de manera opcional en carbono por uno o mas R^8, o R^2 es -NHR^9, -NR^{10}R^{11} o -O-R^{12},

q es 0-2, en donde los valores de R^2 pueden ser los mismos o diferentes,

R^3 es halo, nitro, ciano, hidroxi, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-3}alquilo, C_{2-3}alquenilo, C_{2-3}alquinilo, C_{1-3}alcoxi, C_{1-3}alcanoilo, *N*-(C_{1-3}alquil)amino, *N*,*N*-(C_{1-3}alquil)$_2$amino, C_{1-3}alcanoilamino, *N*-(C_{1-3}alquil)carbamoilo, *N*,*N*-(C_{1-3}alquil)$_2$carbamoilo, C_{1-3}alquilS(O)$_a$ en donde a es 0 a 2, *N*-(C_{1-3}alquil)sulfamoilo o *N*,*N*-(C_{1-3}alquil)$_2$sulfamoilo, en donde R^3 puede sustituirse independientemente de manera opcional en carbono por uno o más R^{13},

n es 0 a 2, en donde los valores de R^3 pueden ser los mismos o diferentes,

R^4 es hidrógeno, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, carbociclilo o un heterociclilo enlazado a carbono, en donde R^4 puede sustituirse de manera opcional en carbono por uno o mas R^{14}, y en donde, si dicho heterociclilo contiene una fraccion -NH-, ese nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de R^{15},

R^5 y R^6 se seleccionan independientemente de hidrógeno, halo, nitro, ciano, hidroxi, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$ en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, *N*-(C_{1-6}

$_6$alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino, C_3 $_8$cicloalquilo o un grupo heterociclico saturado de 4-7 miembros, en donde R^5 y R^6 independientemente uno de otro pueden sustituirse de manera opcional en carbono por uno o mas R^{16}, y en donde, si dicho grupo heterociclico saturado de 4-7 miembros contiene una fraccion -NH-, ese nitrogeno puede sustituirse opcionalmente por un grupo seleccionado de R^{17},

R^7, R^9, R^{10}, R^{11} y R^{12} se seleccionan independientemente de C_1 $_6$alquilo, C_{1-6}alcanoilo, C_{1-6}alquilsulfonilo, C_{2-6}alquenilsulfonilo, C_2 $_6$alquinilsulfonilo, C_{1-6}alcoxicarbonilo, carbamoilo, *N*-(C_1 $_6$alquil)carbamoilo, *N,N*-(C_{1-6}alquil)carbamoilo, carbociclilo, heterociclilo, carbociclil-R^{18} - o heterociclil-R^{19}-, en donde R^7, R^9, R^{10}, R^{11} y R^{12} pueden sustituirse independientemente de manera opcional en carbono por un grupo seleccionado de R^{20}, y en donde, si dicho heterociclilo contiene una fraccion -NH-, ese nitrogeno puede sustituirse opcionalmente por R^{21},

R^{14} y R^{20} se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-6}alquilo, C_2 $_6$alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{2-6}alqueniloxi, C_{2-6}alquiniloxi, C_1 $_6$alcoxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alcoxiC_{1-6}alcoxi, C_{1-6}alcanoilo, C_1 $_6$alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_1 $_6$alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, C_1 $_6$alquilS(O)$_a$ en donde **a** es 0 a 2, C_{1-6}alcoxicarbonilo, *N*-(C_1 $_6$alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino, carbociclilo, heterociclilo, carbociclilC_{1-6}alquil-R^{22}-, heterociclilC_{1-6}alquil-R^{23}-, carbociclil-R^{24}- o heterociclil-R^{25}-, en donde R^{14} y R^{20} pueden sustituirse de manera opcional en carbono por uno o más R^{26}, y en donde, si dicho heterociclilo contiene una fracción -NH-, ese nitrogeno puede sustituirse opcionalmente por un grupo seleccionado de R^{27},

R^{18}, R^{19}, R^{22}, R^{23}, R^{24}, R^{25} se seleccionan independientemente de -O-, -N(R^{28})-, -C(O)-, -N(R^{29})C(O)-, -C(O)N(R^{30})-, -S(O)$_s$-, -SO_2N(R^{31})- o -N(R^{32})SO_2-, en donde **R^{28}, R^{29}, R^{30}, R^{31} y R^{32}** se seleccionan independientemente de hidrógeno o C_{1-6}alquilo y **s** es 0-2,

R^{15}, R^{17}, R^{21} y R^{27} se seleccionan independientemente de C_{1-6}alquilo, C_{1-6}alcanoilo, C_{1-6}alquilsulfonilo, C_{1-6}alcoxicarbonilo, carbamoilo, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)carbamoilo, bencilo, benciloxicarbonilo, benzoilo y fenilsulfonilo, en donde R^{15}, R^{17}, R^{21} y R^{27} independientemente uno de otro pueden sustituirse de manera opcional en carbono por uno o mas R^{33}, y

R^{8}, R^{13}, R^{16}, R^{26} y R^{33} se seleccionan independientemente de halo, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo o *N*-metil-*N*-etilsulfamoilo,
o su sal farmaceuticamente aceptable o éster hidrolizable *in vivo*

En esta especificación el termino "alquilo" incluye grupos alquilo tanto de cadena recta como ramificada, pero las referencias a grupos alquilo individuales tales como "propilo" son específicos de la version de cadena recta unicamente Por ejemplo, "C_{1-6}alquilo" y "C_{1-4}alquilo" incluyen metilo, etilo, propilo, isopropilo y *t*-butilo No obstante, las referencias a grupos alquilo individuales tales como 'propilo' son especificos de la versión de cadena recta unicamente y las referencias a grupos alquilo individuales de cadena ramificada, tales como 'isopropilo', son especificos de la version de cadena ramificada unicamente Una convencion similar se aplica a otros radicales, por ejemplo "carbociclilC_{1-6}alquil-R^{20}" incluye carbociclilmetil-R^{20}, 1-carbociclileti-R^{20} y 2-carbociclileti-R^{20} El término "halo" se refiere a fluoro, cloro, bromo y yodo

Donde se seleccionan sustituyentes opcionales de "uno o mas" grupos hay que entender que esta definicion incluye todos los sustituyentes que se escogen de uno de los grupos especificados o los sustituyentes que se estan seleccionado de dos o mas de los grupos especificados

Un "heterociclilo" es un anillo mono o biciclico saturado, parcialmente saturado o insaturado, que contiene 4-12 atomos de los cuales por lo menos un atomo se escoge de nitrogeno, azufre u oxigeno, el cual, a menos que se especifique lo contrario, puede estar enlazado a carbono o nitrogeno, en donde un grupo $-CH_2-$ puede reemplazarse de manera opcional por un -C (O)-, un atomo de nitrógeno de anillo puede llevar opcionalmente un grupo C_{1-6}alquilo y formar un compuesto cuaternario o un atomo de nitrogeno y/o azufre de anillo puede oxidarse opcionalmente para formar el *N*-oxido y los S-oxidos Ejemplos y valores apropiados del termino "heterociclilo" son morfolino, piperidilo, piridilo, piranilo, pirrolilo, isotiazolilo, indolilo, quinolilo, tienilo, 1,3-benzodioxolilo, tiadiazolilo, piperazinilo, tiazolidinilo, pirrolidinilo, tiomorfolino, pirrolinilo, homopiperazinilo, 3,5-dioxapiperidinilo, tetrahidropiranilo, imidazolilo, pirimidilo, pirazinilo, piridazinilo, isoxazolilo, *N*-metilpirrolilo, 4-piridona, 1-isoquinolona, 2-pirrolidona, 4-tiazolidona, piridin-*N*-oxido y quinolin-*N*-oxido En un aspecto de la invencion un "heterociclilo" es un anillo mono o biciclico saturado, parcialmente saturado o insaturado, que contiene 5 o 6 atomos de los cuales por lo menos un atomo se selecciona de nitrogeno, azufre u oxigeno, el cual puede, a menos que se indique lo contrario, enlazarse a carbono o nitrógeno, en donde un grupo $-CH_2-$ puede reemplazarse de manera opcional por un -C(O)-, y un atomo de azufre de anillo puede oxidarse de manera opcional para formar los S-oxidos

Un "carbociclilo" es un anillo de carbono mono o biciclico saturado, parcialmente saturado o insaturado, que contiene 3-12 átomos, en donde un grupo $-CH_2-$ puede reemplazarse de manera opcional por un -C(O)- Particularmente "carbociclilo" es un anillo monociclico que contiene 5 o 6 atomos o un anillo biciclico que contiene 9 o 10 atomos Valores apropiados para "carbociclilo" incluyen ciclopropilo, ciclobutilo, 1-oxociclopentilo, ciclopentilo, ciclopentenilo, ciclohexilo, ciclohexenilo, fenilo, naftilo, tetralinilo, indanilo o 1-oxoindanilo

Un "grupo heterocíclico saturado de 4-7 miembros" es un anillo monociclico saturado que contiene 4-7 átomos, de los cuales por lo menos

un átomo se selecciona de nitrogeno, azufre u oxigeno, el cual puede, a menos que se especifique lo contrario, enlazarse a carbono o nitrogeno, en donde un grupo -CH_2- puede reemplazarse de manera opcional por un -C(O)- y un átomo de azufre puede oxidarse de manera opcional para formar los S-óxidos Ejemplos y valores apropiados del termino "grupo heterociclico saturado de 4-7 miembros" son morfolino, piperidilo, 1,4-dioxanilo, 1,3-dioxolanilo, 1,2-oxatiolanilo, imidazolidinilo, pirazolidinilo, piperazinilo, tiazolidinilo, pirrolidinilo, tiomorfolino, homopiperazinilo y tetrahidropiranilo

Anillo A es "un anillo saturado de 4-7 miembros, enlazado a nitrogeno, que contiene opcionalmente un átomo adicional de nitrógeno, oxigeno o azufre" Un "anillo saturado de 4-7 miembros, enlazado a nitrogeno, que contiene opcionalmente un atomo adicional de nitrogeno, oxigeno o azufre" es un anillo monociclico saturado, que contiene 4-7 atomos enlazados a la fraccion fenilo de formula (I) via un atomo de nitrógeno contenido en el anillo, el anillo opcionalmente contiene un heteroatomo adicional seleccionado de nitrógeno, azufre u oxigeno, en donde un grupo -CH_2- puede reemplazarse de manera opcional por un -C(O)-, y el atomo de azufre opcional puede oxidarse de manera opcional para formar los S-óxidos

Ejemplos de "$C_{1\ 3}$alquilo" incluyen metilo, etilo, propilo e isopropilo Un ejemplo de "$C_{1\text{-}6}$alcanoiloxi" es acetoxi Ejemplos de "$C_{1\ 6}$alcoxicarbonilo" incluyen metoxicarbonilo, etoxicarbonilo, *n*- y *t*-butoxicarbonilo Ejemplos de "$C_{1\text{-}6}$alcoxi" y "$C_{1\ 3}$alcoxi" incluyen metoxi, etoxi y propoxi Ejemplos de "$C_{1\text{-}6}$alcanoilamino" y "$C_{1\text{-}3}$alcanoilamino" incluyen formamido, acetamido y propionilamino Ejemplos de "$C_{1\ 6}$alquilS(O)$_a$ en donde **a** es 0 a 2" y "$C_{1\ 3}$alquilS(O)$_a$, en donde **a** es 0 a 2" incluye metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo y etilsulfonilo Ejemplos de "$C_{1\text{-}6}$alquilS(O)$_r$ en donde **r** es 1 a 2" incluyen metilsulfinilo, etilsulfinilo, mesilo y etilsulfonilo Ejemplos de "$C_{1\text{-}6}$alcanoilo" y "$C_{1\ 3}$alcanoilo" incluyen propionilo y acetilo Ejemplos de "*N*-$C_{1\text{-}6}$alquilamino" y "*N*-$C_{1\ 3}$alquilamino" incluyen metilamino y etilamino Ejemplos de "*N*,*N*-

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(C_{1-6}alquil)$_2$amino" y "*N*,*N*-(C_{1-3}alquil)$_2$amino" incluyen di-*N*-metilamino, di-(*N*-etil)amino y *N*-etil-*N*-metilamino Ejemplos de "C_{2-6}alquenilo" y "C_{2-3}alquenilo" son vinilo, alilo y 1-propenilo Ejemplos de "C_{2-6}alquinilo" y "C_{2-3}alquinilo" son etinilo, 1-propinilo y 2-propinilo Ejemplos de "*N*-(C_{1-6}alquil)sulfamoilo" y "*N*-(C_{1-3}alquil)sulfamoilo" son *N*- (metil)sulfamoilo y *N*-(etil)sulfamoilo Ejemplos de "*N*,*N*-(C_{1-6}alquil)$_2$sulfamoilo" y "*N*,*N*-(C_{1-3}alquil)$_2$sulfamoilo" son *N*,*N*-(dimetil)sulfamoilo y *N*-(metil)-*N*-(etil)sulfamoilo Ejemplos de "*N*-(C_{1-6}alquil)carbamoilo" y "*N*-(C_{1-3}alquil)carbamoilo" son metilaminocarbonilo y etilaminocarbonilo Ejemplos de "*N*,*N*-(C_{1-6}alquil)$_2$carbamoilo" y "*N*,*N*-(C_{1-3}alquil)$_2$carbamoilo" son dimetilaminocarbonilo y metiletilaminocarbonilo Ejemplos de "C_{3-8}cicloalquilo" son ciclopropilo, ciclobutilo, ciclopropilo y ciclohexilo Ejemplos de "C_{1-6}alquilsulfonilamino" incluyen metilsulfonilamino, isopropilsulfonilamino y *t*-butilsulfonilamino Ejemplos de "C_{1-6}alquilsulfonilo" incluyen metilsulfonilo, isopropilsulfonilo y *t*-butilsulfonilo Ejemplos de "C_{2-6}alquenilsulfonilo" incluyen vinilsulfonilo, alilsulfonilo y 1-propenilsulfonilo Ejemplos de "C_{2-6}alquinilsulfonilo" incluyen etinilsulfonilo, 1-propinilsulfonilo y 2-propinilsulfonilo Ejemplos de "C_{1-6}alcoxiC_{1-6}alcoxi" incluyen metoxietoxi, 2-etoxipropoxi y 2-isopropoxibutoxi Ejemplos de "C_{1-6}alcoxiC_{1-6}alcoxiC_{1-6}alcoxi" incluyen metoxietoximetoxi, 2-etoxipropoximetoxi y 3-(2-isopropoxibutoxi)etoxi Ejemplos de "C_{2-6}alqueniloxi" incluyen viniloxi y aliloxi Ejemplos de "C_{2-6}alquiniloxi" incluyen etiniloxi y 2-propiniloxi

Una sal apropiada farmacéuticamente aceptable de un compuesto de la invencion es, por ejemplo, una sal de adicion de acido de un compuesto de la invencion que es suficientemente basica, por ejemplo, una sal de adicion de ácido con, por ejemplo, un acido organico o inorganico, por ejemplo acido clorhídrico, bromhidrico, sulfúrico, fosfórico, trifluoroacetico, citrico o maleico Adicionalmente una sal apropiada farmaceuticamente aceptable de un compuesto de la invencion que es suficientemente acida es una sal de metal alcalino, por ejemplo una sal de sodio o potasio, una sal de metal alcalinotérreo, por ejemplo una sal de

calcio o magnesio, una sal de amonio o una sal con una base organica que proporciona un catión fisiológicamente aceptable, por ejemplo una sal con metilamina, dimetilamina, trimetilamina, piperidina, morfolina o tris-(2-hidroxietil)amina

Un ester hidrolizable *in vivo* de un compuesto de la formula (I) que contiene un grupo carboxi o hidroxi es, por ejemplo, un ester farmaceuticamente aceptable que se hidroliza en el cuerpo humano o animal para producir el ácido o alcohol original Esteres apropiados farmaceuticamente aceptables para carboxi incluyen ésteres de C_{1-6}alcoximetilo por ejemplo esteres de metoximetilo, C_{1-6}alcanoiloximetilo por ejemplo pivaloiloximetilo, ésteres de ftalidilo, esteres de C_{3-8}cicloalcoxicarboniloxiC_{1-6}alquilo por ejemplo 1-ciclohexilcarboniloxietilo, esteres de 1,3-dioxolen-2-onilmetilo por ejemplo 5-metil-1,3-dioxolen-2-onilmetilo, y esteres de C_{1-6}alcoxicarboniloxietilo por ejemplo 1-metoxicarboniloxietilo y pueden formarse en cualquier grupo carboxi en los compuestos de esta invencion

Un ester hidrolizable *in vivo* de un compuesto de la formula (I) que contiene un grupo hidroxi incluye esteres inorganicos tales como esteres de fosfato y éteres de α-aciloxialquilo y compuestos relacionados que como resultado de la hidrolisis *in vivo* del ester se descomponen para producir el grupo hidroxi original Ejemplos de eteres de α-aciloxialquilo incluyen acetoximetoxi y 2,2-dimetilpropioniloxi-metoxi Una seleccion de grupos que forman éster hidrolizable *in vivo* para hidroxi incluyen alcanoilo, benzoilo, fenilacetilo y benzoilo y fenilacetilo sustituido, alcoxicarbonilo (para producir esteres de carbonato de alquilo), dialquilcarbamoilo y *N*-(dialquilaminoetil)-*N*-alquilcarbamoilo (para producir carbamatos), dialquilaminoacetilo y carboxiacetilo Ejemplos de sustituyentes en benzoilo incluyen morfolino y piperazino enlazados desde un atomo de nitrogeno del anillo mediante un grupo metileno a la posicion 3 o 4 del anillo benzoilo

Algunos compuestos de la formula (I) pueden tener centros quirales y/o centros isoméricos geometricos (isómeros E y Z), y hay que entender

que la invencion abarca todos aquellos isomeros opticos, diastereoisomeros e isómeros geométricos que poseen actividad inhibidora CDK

La invencion se relaciona con cualesquiera y todas las formas tautoméricas de los compuestos de la fórmula (I) que poseen actividad inhibidora CDK En particular, el lector experto observara que cuando R^4 es hidrogeno, el anillo imidazol como se describe en formula (I) puede tautomerizarse

Hay que entender igualmente que ciertos compuestos de la formula (I) pueden existir en formas solvatadas asi como no solvatadas tales como, por ejemplo, formas hidratadas Hay que entender que la invencion abarca todas las formas solvatadas similares que poseen actividad inhibidora CDK

Valores particulares de grupos variables son los siguientes Tales valores pueden usarse, donde se estime apropiado, con cualquiera de las definiciones, reivindicaciones o incorporaciones definidas mas arriba en el texto o a partir de ahora.

Anillo A es un anillo saturado de 4-7 miembros, enlazado a nitrogeno, que contiene opcionalmente un átomo adicional de nitrogeno u oxígeno, en donde, si anillo A contiene un atomo adicional de nitrogeno, ese nitrogeno puede sustituirse opcionalmente por R^7, en donde

R^7 se selecciona de C_{1-6}alcanoilo, C_{1-6}alquilsulfonilo, C_{2-6}alquenilsulfonilo, carbociclil-R^{18}- o heterociclil-R^{19}-, en donde R^7 puede sustituirse independientemente de manera opcional en carbono por un grupo seleccionado de R^{20}, y en donde si dicho heterociclilo contiene una fracción -NH-, ese nitrogeno puede sustituirse opcionalmente por R^{21},

R^{18} y R^{19} son -C(O)-,

R^{20} se selecciona de halo, ciano, hidroxi, C_{1-6}alcoxi, C_{2-6}alquiniloxi, C_{1-6}alcanoiloxi, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alquilS(O)$_a$ en donde a es 2 o heterociclilo, en donde R^{20} puede sustituirse de manera opcional en carbono por uno o más R^{26},

R^{21} es C_{1-6}alquilo, y

R^{26} es hidroxi

Anillo A es un anillo saturado de 4-6 miembros, enlazado a nitrogeno, que contiene opcionalmente un átomo adicional de nitrogeno u oxigeno, en donde, si anillo A contiene un atomo adicional de nitrogeno es nitrogeno puede sustituirse opcionalmente por R^7, en donde

R^7 se selecciona de C_{1-6}alcanoilo, C_{1-6}alquilsulfonilo, C_{2-6}alquenilsulfonilo, carbociclil-R^{18}- o heterociclil-R^{19}-, en donde R^7 puede sustituirse independientemente de manera opcional en carbono por un grupo seleccionado de R^{20}, y en donde si dicho heterociclilo contiene una fraccion -NH-, ese nitrógeno puede sustituirse opcionalmente por R^{21},

R^{18} y R^{19} are -C(O)-,

R^{20} se selecciona de halo, ciano, hidroxi, C_{1-6}alcoxi, C_{2-6}alquiniloxi, C_{1-6}alcanoiloxi, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alquilS(O)$_a$ en donde a es 2 o heterociclilo, en donde R^{20} puede sustituirse de manera opcional en carbono por uno o mas R^{26},

R^{21} es C_{1-6}alquilo, y

R^{26} es hidroxi

Anillo A es un anillo saturado de 4-7 miembros, enlazado a nitrogeno, que contiene opcionalmente un átomo adicional de nitrogeno, oxigeno o azufre, en donde, si anillo A contiene un atomo adicional de nitrogeno, ese nitrogeno puede sustituirse opcionalmente por R^7, en donde

R^7 se selecciona de C_{1-6}alcanoilo, C_{1-6}alquilsulfonilo, C_{2-6}alquenilsulfonilo, carbociclil-R^{18}- o heterociclil-R^{19}-, en donde R^7 puede sustituirse independientemente de manera opcional en carbono por un grupo seleccionado de R^{20}, y en donde, si dicho heterociclilo contiene una fraccion –NH-, ese nitrógeno puede sustituirse opcionalmente por R^{21},

R^{20} se selecciona de halo, ciano, hidroxi, C_{1-6}alcoxi, C_{2-6}alquiniloxi, C_{1-6}alcanoiloxi, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alquilS(O)$_a$, en donde a es 2 o heterociclilo, en donde R^{20} puede sustituirse de manera opcional en carbono por uno o mas R^{26},

R^{18} y R^{19} son -C(O)-,

R^{21} es C_{1-6}alquilo, y

R^{26} es hidroxi

Anillo A es un anillo saturado de 6 miembros, enlazado a nitrogeno, que contiene opcionalmente un atomo adicional de nitrogeno, en donde, si anillo A contiene un átomo adicional de nitrogeno, ese nitrogeno puede sustituirse opcionalmente por R^7, en donde

R^7 se selecciona de C_{1-6}alcanoilo, C_{1-6}alquilsulfonilo y C_{2-6}alquenilsulfonilo, en donde R^7 puede sustituirse de manera opcional en carbono por un grupo seleccionado de R^{20}, en donde

R^{20} se selecciona de hidroxi, C_{1-6}alcoxi, C_{1-6}alcanoiloxi y *N*,*N*-(C_{1-6}alquil)$_2$amino

Anillo A es piperazin-1-ilo, morfolino, pirrolidinilo o azetidinilo, en donde dicho piperazin-1-ilo puede sustituirse de manera opcional en nitrógeno por R^7, en donde

R^7 se selecciona de acetilo, propionilo, 2,2-dimetilpropanoilo, 3-metilbutanoilo, butirilo, isobutirilo, mesilo, etilsulfonilo, etenilsulfonilo, ciclopropil-R^{18}-, tetrahidrofuranil-R^{19}- o pirrolidinil-R^{19}-, en donde R^7 puede sustituirse independientemente de manera opcional en carbono por un grupo seleccionado de R^{20}, y en donde, si dicho heterociclilo contiene una fracción -NH-, ese nitrogeno puede sustituirse opcionalmente por R^{21},

R^{18} y R^{19} son -C(O)-,

R^{20} se selecciona de fluoro, cloro, ciano, hidroxi, metoxi, prop-2-in-1-iloxi, acetoxi, dimetilamino, dietilamino, mesilo, tetrazolilo, pirrolidinilo, morfolino, azetidinilo, en donde R^{20} puede sustituirse de manera opcional en carbono por uno o más R^{26},

R^{21} es metilo, y

R^{26} es hidroxi

Anillo A es piperazin-1-ilo o morfolino, en donde dicho piperazinilo puede sustituirse de manera opcional en nitrogeno por R^7, en donde

R^7 se selecciona de acetilo, propionilo, 2-metilpropionilo, 2,2-dimetilpropionilo, butanoilo, 3-metilbutanoilo, mesilo, vinilsulfonilo, ciclopropil-R^{18}-, pirrolidin-2-il-R^{19}-, tetrahidrofuran-2-il-R^{19}- o tetrahidrofuran-3-il-R^{19}-, en donde R^7 puede sustituirse independientemente

de manera opcional en carbono por un grupo seleccionado de R^{20}, y en donde, si dicho heterociclilo contiene una fracción -NH-, ese nitrogeno puede sustituirse opcionalmente por R^{21},

R^{20} se selecciona de fluoro, cloro, ciano, hidroxi, metoxi, 2-propiniloxi, acetoxi, dimetilamino, dietilamino, mesilo, azetidin-1-ilo, pirrolidin-1-ilo, morfolino, tetrazol-1-ilo o tetrazol-5-ilo, en donde R^{20} puede sustituirse de manera opcional en carbono por uno o más R^{26},

R^{18} y R^{19} son -C(O)-,

R^{21} es metilo, y

R^{26} es hidroxi

Anillo A es morfolino o piperazin-1-ilo, en donde, si anillo A es piperazin-1-ilo, la fraccion -NH- puede sustituirse de manera opcional por R^7, en donde

R^7 se selecciona de acetilo, metilsulfonilo, etilsulfonilo y vinilsulfonilo, en donde R^7 puede sustituirse de manera opcional en carbono por un grupo seleccionado de R^{20}, en donde

R^{20} se selecciona de hidroxi, metoxi, acetoxi y dimetilamino

Anillo A, R^2 y q juntos forman piperazin-1-ilo, morfolino, 4-mesilpiperazin-1-ilo, 4-acetilpiperazin-1-ilo, 4-(2-acetoxiacetil)piperazin-1-ilo, 4-(2-hidroxiacetil)piperazin-1-ilo, 4-(2-cloroacetil)piperazin-1-ilo,4-(2-metoxiacetil)piperazin-1-ilo, (3-metoxipropanoil)piperazin-1-ilo, (3-hidroxi-3-metilbutanoil)piperazin-1-ilo, (3-hidroxi-2,2-dimetilpropanoil) piperazin-1-ilo, ((R)-3-metil-2-hidroxibutanoil)piperazin-1-ilo, ((S)-3-metil-2-hidroxibutanoil)piperazin-1-ilo, 4-(2-dimetilaminoacetil)piperazin-1-ilo, 4-[2-(dimetilamino)etilsulfonil]piperazin-1-ilo, 4-[2-(metoxi)etilsulfonil] piperazin-1-ilo, 4-[2-(hidroxi)etilsulfonil]piperazin-1-ilo, 4-(ciclopropilcarbonil)piperazin-1-ilo, 4-(1-hidroxiciclopropilcarbonil) piperazin-1-ilo, 4-(1-cianociclopropilcarbonil)piperazin-1-ilo, 4-(2-hidroxi-2-metilpropanoil)piperazin-1-ilo, 4-((R)-2-hidroxipropanoil)piperazin-1-ilo, 4-((S)-2-hidroxipropanoil)piperazin-1-ilo, 4-((R)-2-metoxipropanoil) piperazin-1-ilo, 4-((S)-2-metoxipropanoil)piperazin-1-ilo, 4-((R)-tetrahidrofuran-2-ilcarbonil)piperazin-1-ilo, 4-((S)-tetrahidrofuran-2-

ılcarbonıl)pıperazın-1-ılo, 4-(ısobutırıl)pıperazın-1-ılo, 4-((R)-2-hıdroxıbutanoıl)pıperazın-1-ılo, 4-((S)-2-hıdroxıbutanoıl)pıperazın-1-ılo, (R)-3-acetılamınopırrolıdın-1-ılo, (S)-3-acetılamınopırrolıdın-1-ılo, (R)-2-(cıclopropılamınocarbonıl)pırrolıdın-1-ılo, (R)-2-(*N*-metılcarbamoıl) pırrolıdın-1-ılo, (S)-2-(*N*,*N*-dımetılcarbamoıl)pırrolıdın-1-ılo, 4-(etenılsulfonıl)pıperazın-1-ılo, 4-[2-(2-propın-1-ıloxı)acetıl]pıperazın-1-ılo, 4-(tetrahıdrofuran-3-ılcarbonıl)pıperazın-1-ılo, 4-(3-dımetılamınopropanoıl) pıperazın-1-ılo, 4[2-(*N*-metıl-*N*-hıdroxımetılamıno)acetıl]pıperazın-1-ılo, 4-[3-hıdroxı-2-(hıdroxımetıl)propanoıl]pıperazın-1-ılo, 4-[2-(1,2,3,4-tetrazol-1-ıl)acetıl]pıperazın-1-ılo, 4-[2-(1,2,3,4-tetrazol-5-ıl)acetıl]pıperazın-1-ılo, 4-(1-metıl-L-propıl)pıperazın-1-ılo, 4-[2-(mesıl)acetıl]pıperazın-1-ılo, 4(2,2-dıfluoroacetıl)pıperazın-1-ılo, 4[2-(pırrolıdın-1-ıl)acetıl]pıperazın-1-ılo, 4-[2-(morfolıno)acetıl]pıperazın-1-ılo, 4-[2-(dıetılamıno)acetıl] pıperazın-1-ılo, 4(propıonıl)pıperazın-1-ılo, 4-(3-hıdroxıpropıonıl) pıperazın-1-ılo, 4-[2-azetıdın-1-ıl)acetıl]pıperazın-1-ılo, (R)-3-amınopırrolıdın-1-ılo, (S)-3-amınopırrolıdın-1-ılo, (3*R*,5*S*)-4-acetıl-3,5-dımetılpıperazın-1-ılo, (2*S*,5*R*)-4-acetıl-2,5-dımetılpıperazın-1-ılo, (2*RS*,6*SR*)-2,6-dımetılmorfolın-4-ıl] fenılo, 3-hıdroxıazetıdın-1-ılo, 3-acetılamınoazetıdın-1-ılo, 3-(2-hıdroxıacetılamıno)azetıdın-1-ılo, 3-mesılamınoazetıdın-1-ılo, 3-mesıloxıazetıdın-1-ılo, 3-azıdoazetıdın-1-ılo, 3-amınoazetıdın-1-ılo, (3*R*)-3-{[(2*S*)-2-hıdroxıpropanoıl]amıno}pırrolıdın-1-ılo, (3*S*)-3-{[(2S)-2-hıdroxıpropanoıl]amıno}pırrolıdın-1-ılo, (3*S*)-3-(glıcoloılamıno)pırrolıdın-1-ılo y (3*R*)-3-(glıcoloılamıno)pırrolıdın-1-ılo

Anıllo A es [4-(2-acetoxıacetıl)pıperazın-1-ılo, [4-(hıdroxıacetıl)pıperazın-1-ılo, 4-((*R*)-2-hıdroxıbutanoıl)pıperazın-1-ılo, 4-((R)-2-hıdroxıpropıonıl)pıperazın-1-ılo, 4-((R)-2-metoxıpropıonıl) pıperazın-1-ılo, 4-((R)-3-metıl-2-hıdroxıbutanoıl)pıperazın-1-ılo, 4-((*R*)-tetrahıdrofur-2-ılcarbonıl)pıperazın-1-ılo, 4-((*S*)-2-hıdroxıbutanoıl) pıperazın-1-ılo, 4-((*S*)-2-metoxıpropıonıl)pıperazın-1-ılo, 4-((*S*)-3-metıl-2-hıdroxıbutanoıl)pıperazın-1-ılo, 4-((*S*)-tetrahıdrofur-2-ılcarbonıl) pıperazın-1-ılo, 4-(1-cıanocıcloprop-1-ılcarbonıl)pıperazın-1-ılo, 4-(1-hıdroxıcıcloprop-1-ılcarbonıl)pıperazın-1-ılo, 4-(1-metıl-L-prolılcarbonıl)

piperazin-1-ilo, 4-(2-(R)-tetrahidrofur-2-ilcarbonil)piperazin-1-ilo, 4-(2-(S)-2-hidroxipropionil)piperazin-1-il)piperazin-1-ilo, 4-(2-(S)-tetrahidrofur-2-il)piperazin-1-ilo, 4-(2,2-difluoroacetil)piperazin-1-ilo, 4-(2-acetoxiacetil) piperazin-1-ilo, 4-(2-dimetilaminoacetil) piperazin-1-ilo, 4-(2-dimetilaminoetilsulfonil)piperazin-1-ilo, 4-(2-hidroxi-2-metilpropionil) piperazin-1-ilo, 4-(2-hidroxiacetil)piperazin-1-ilo, 4-(2-hidroxietilsulfonil) piperazin-1-ilo, 4-(2-hidroxipropionil)piperazin-1-ilo, 4-(2-mesilacetil) piperazin-1-ilo, 4-(2-metoxiacetil)piperazin-1-ilo, 4-(2-metoxietilsulfonil) piperazin-1-ilo, 4-(2-metil-2-hidroxipropionil)piperazin-1-ilo, 4-(2-metilpropionil)piperazin-1-ilo, 4- (2-morfolinoacetil)piperazin-1-ilo, 4-(2-pirrolidin-1-ilacetil)piperazin-1-ilo, 4-(3-dimetilaminopropionil)piperazin-1-ilo, 4-(3-hidroxi-2,2-dimetilpropionil)piperazin-1-ilo, 4-(3-hidroxipropionil)piperazin-1-ilo, 4- (3-metoxipropionil)piperazin-1-ilo, 4-(3-metil-3-hidroxibutanoil)piperazin-1-ilo, 4-(4-hidroxibutanoil)piperazin-1-ilo, 4-(acetoxiacetil)piperazin-1-ilo, 4-(acetil)piperazin-1-ilo, 4-(azetidin-1-ilacetil)piperazin-1-ilo, 4-(cloroacetil)piperazin-1-ilo, 4-(ciclopropil) piperazin-1-ilo, 4-(propionil)piperazin-1-ilo, 4-(tetrahidrofur-3-ilcarbonil) piperazin-1-ilo,4-(vinilsulfonil)piperazin-1-ilo, 4-[2-(1*H*-tetrazol-5-il)acetil) piperazin-1-ilo, 4-[2-(2-propiniloxi)acetil]piperazin-1-ilo, 4-[2-(*N*-hidroximetil-*N*-metilamino)acetil]piperazin-1-ilo, 4-[2-(tetrazol-1-il)acetil] piperazin-1-ilo, 4-acetilpiperazin-1-ilo, 4-mesilpiperazin-1-ilo, morfolino, y piperazin-1-ilo

Anillo A es 4-metilsulfonilpiperazin-1-ilo, 4-vinilsulfonilpiperazin-1-ilo, 4-acetilpiperazin-1-ilo, 4-(acetoxiacetil)piperazin-1-ilo, 4-(hidroxiacetil) piperazin-1-ilo, 4-(dimetilaminoacetil)piperazin-1-ilo, 4-(2-dimetilaminoetilsulfonil)piperazin-1-ilo, 4-(2-metoxietilsulfonil)piperazin-1-ilo, 4-(2-hidroxietilsulfonil)piperazin-1-ilo, piperazin-1-ilo o morfolino

R^1 es halo o C_{1-6}alquilo

R^1 es fluoro, cloro o metilo

p es 0-2, en donde los valores de R^1 pueden ser los mismos o diferentes

p es 0 o 1

p es 1

p es 0

R^2 se selecciona de hidroxi, amino, azido, C_{1-6}alquilo, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, carbociclil-R^{34}-, -NHR^9 o -O-R^{12},

R^9 y R^{12} se seleccionan independientemente de C_{1-6}alcanoilo o C_{1-6}alquilsulfonilo, en donde R^9 y R^{12} pueden sustituirse independientemente de manera opcional en carbono por un grupo seleccionado de R^{20},

R^{20} es hidroxi, y

R^{34} es -N(R^{29})C(O)-, en donde R^{29} es hidrogeno

R^2 se selecciona de hidroxi, amino, azido, metilo, *N*-metilcarbamoilo, *N*,*N*-dimetilcarbamoilo, ciclopropil-R^{34}-, -NHR^9 o -O-R^{12},

R^9 y R^{12} se seleccionan independientemente de acetilo, propionilo o mesilo, en donde R^9 y R^{12} pueden sustituirse independientemente de manera opcional en carbono por un grupo seleccionado de R^{20},

R^{34} es hidroxi, y

R^{34} es -N(R^{29})C(O)-, en donde R^{29} es hidrogeno

R^2 se selecciona de hidroxi, amino, azido, metilo, *N*-metilcarbamoilo, *N*,*N*-dimetilcarbamoilo, acetamido, {[(2*S*)-2-hidroxipropanoil]amino}, glicoloilamino, mesilamino, 2-hidroxiacetamido, mesiloxi o *N*-ciclopropilcarbamoilo

q es 0 o 1

q es 2

q es 1

q es 0

R^3 es halo

R^3 es fluoro o cloro

R^3 es 5-fluoro o 5-cloro

R^3 es 5-fluoro o 5-cloro

n es 0 o 1

n es 1

n es 0

R^4 es C_{1-6}alquilo o carbociclilo, en donde R^4 puede sustituirse de manera opcional en carbono por uno o más R^{14}, en donde

R^{14} es carbociclilo

R^4 es C_{1-4}alquilo o ciclobutilo, en donde R^4 puede sustituirse de manera opcional en carbono por uno o mas R^{14}, en donde

R^{14} es ciclopropilo

R^4 es etilo, isopropilo, isobutilo, ciclobutilo o ciclopropilmetilo

R^4 es isopropilo

R^5 y R^6 se seleccionan independientemente de hidrogeno o C_{1-6}alquilo, en donde R^5 y R^6, independientemente uno de otro, pueden sustituirse de manera opcional en carbono por uno o mas R^{16}, en donde

R^{16} se selecciona de metoxi

R^5 y R^6 se seleccionan independientemente de hidrogeno metilo, etilo o propilo, en donde R^5 y R^6, independientemente uno de otro, pueden sustituirse de manera opcional en carbono por uno o más R^{16}, en donde

R^{16} se selecciona de metoxi

R^5 y R^6 se seleccionan independientemente de hidrogeno, metilo, etilo, metoximetilo, propilo

R^5 es C_{1-6}alquilo, en donde R^5 puede sustituirse de manera opcional en carbono por uno o mas R^{16}, en donde

R^{16} es metoxi

R^5 es C_{1-4}alquilo, en donde R^5 puede sustituirse de manera opcional en carbono por uno o más R^{16}, en donde

R^{16} es metoxi

R^5 es metilo, etilo, propilo o metoximetilo

R^5 es metilo

R^6 es hidrógeno

R^4 es isopropilo, R^5 es metilo y R^6 es hidrogeno

Por lo tanto, en un aspecto adicional de la invencion, se provee un compuesto de fórmula (I) (como se describe mas arriba) en donde

Anillo A es un anillo saturado de 4-7 miembros, enlazado a nitrogeno, que contiene opcionalmente un atomo adicional de nitrogeno u

oxigeno, en donde, si anillo A contiene un átomo adicional de nitrogeno, ese nitrogeno puede sustituirse opcionalmente por R^7,

R^1 es halo o C_{1-6}alquilo,

p es 0 o 1,

R^2 se selecciona de hidroxi, amino, azido, C_{1-6}alquilo, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, carbociclil-R^{34}-, -NHR^9 o -O-R^{12},

q es 0-2, en donde los valores de R^2 pueden ser los mismos o diferentes,

R^3 es halo,

n es 0 o 1,

R^4 es C_{1-6}alquilo o carbociclilo, en donde R^4 puede sustituirse de manera opcional en carbono por uno o más R^{14},

R^5 y R^6 se seleccionan independientemente de hidrógeno o C_{1-6}alquilo, en donde R^5 y R^6, independientemente uno de otro, pueden sustituirse de manera opcional en carbono por uno o mas R^{16},

R^7 se selecciona de C_{1-6}alcanoilo, C_{1-6}alquilsulfonilo, C_{2-6}alquenilsulfonilo, carbociclil-R^{18}- o heterociclil-R^{19}-, en donde R^7 puede sustituirse independientemente de manera opcional en carbono por un grupo seleccionado de R^{20}, y en donde, si dicho heterociclilo contiene una fraccion -NH-, ese nitrógeno puede sustituirse opcionalmente por R^{21},

R^9 y R^{12} se seleccionan independientemente de C_{1-6}alcanoilo o C_{1-6}alquilsulfonilo, en donde R^9 y R^{12} pueden sustituirse independientemente de manera opcional en carbono por un grupo seleccionado de R^{20},

R^{14} es carbociclilo,

R^{16} se selecciona de metoxi,

R^{18} y R^{19} son -C(O)-,

R^{20} se selecciona de halo, ciano, hidroxi, C_{1-6}alcoxi, C_{2-6}alquiniloxi, C_{1-6}alcanoiloxi, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alquilS(O)$_a$, en donde a es 2 o heterociclilo, en donde R^{20} puede sustituirse de manera opcional en carbono por uno o más R^{26},

R^{21} es C_{1-6}alquilo,

R^{26} es hidroxi, o

R^{34} es -N(R^{29})C(O)-, en donde R^{29} es hidrogeno,

o su sal farmaceuticamente aceptable o ester hidrolizable *in vivo*

Por lo tanto, en un aspecto adicional de la invencion, se provee un compuesto de formula (I) (como se describe mas arriba) en donde

Anillo A, R^2 y q juntos forman piperazin-1-ilo, morfolino, 4-mesilpiperazin-1-ilo, 4-acetilpiperazin-1-ilo, 4-(2-acetoxiacetil)piperazin-1-ilo, 4-(2-hidroxiacetil)piperazin-1-ilo, 4-(2-cloroacetil)piperazin-1-ilo, 4-(2-metoxiacetil)piperazin-1-ilo, (3-metoxipropanoil)piperazin-1-ilo, (3-hidroxi-3-metilbutanoil)piperazin-1-ilo, (3-hidroxi-2,2-dimetilpropanoil) piperazin-1-ilo, ((R)-3-metil-2-hidroxibutanoil)piperazin-1-ilo, ((S)-3-metil-2-hidroxibutanoil)piperazin-1-ilo, 4-(2-dimetilaminoacetil)piperazin-1-ilo, 4-[2-(dimetilamino)etilsulfonil] piperazin-1-ilo, 4-[2-(metoxi)etilsulfonil] piperazin-1-ilo, 4-[2-(hidroxi)etilsulfonil]piperazin-1-ilo, 4-(ciclopropilcarbonil)piperazin-1-ilo, 4-(1-hidroxiciclopropilcarbonil) piperazin-1-ilo, 4-(1-cianociclopropilcarbonil)piperazin-1-ilo, 4-(2-hidroxi-2-metilpropanoil)piperazin-1-ilo, 4-((R)-2-hidroxipropanoil)piperazin-1-ilo, 4-((S)-2-hidroxipropanoil)piperazin-1-ilo, 4-((R)-2-metoxipropanoil) piperazin-1-ilo, 4-((S)-2-metoxipropanoil)piperazin-1-ilo, 4-((R)-tetrahidrofuran-2-ilcarbonil)piperazin-1-ilo, 4-((S)-tetrahidrofuran-2-ilcarbonil)piperazin-1-ilo, 4-(isobutiril)piperazin-1-ilo, 4-((R)-2-hidroxibutanoil)piperazin-1-ilo, 4-((S)-2-hidroxibutanoil)piperazin-1-ilo, (R)-3-acetilaminopirrolidin-1-ilo, (S)-3-acetilaminopirrolidin-1-ilo, (R)-2-(ciclopropilaminocarbonil)pirrolidin-1-ilo (R)-2-(*N*-metilcarbamoil) pirrolidin-1-ilo, (S)-2-(*N*,*N*-dimetilcarbamoil)pirrolidin-1-ilo, 4-(etenilsulfonil)piperazin-1-ilo, 4-[2-(2-propin-1-iloxi)acetil]piperazin-1-ilo, 4-(tetrahidrofuran-3-ilcarbonil)piperazin-1-ilo, 4-(3-dimetilaminopropanoil)piperazin-1-ilo, 4-[2-(*N*-metil-*N*-hidroximetilamino)acetil]piperazin-1-ilo, 4-[3-hidroxi-2-(hidroximetil) propanoil]piperazin-1-ilo, 4-[2-(1,2,3,4-tetrazol-1-il)acetil]piperazin-1-ilo, 4-[2-(1,2,3,4-tetrazol-5-il)acetil]piperazin-1-ilo, 4-(1-metil-L-prolil) piperazin-1-ilo, 4-[2-(mesil)acetil]piperazin-1-ilo, 4-(2,2-difluoroacetil)

piperazin-1-ilo, 4-[2-(pirrolidin-1-il)acetil]piperazin-1-ilo, 4-[2-(morfolino) acetil]piperazin-1-ilo, 4-[2-(dietilamino)acetil]piperazin-1-ilo, 4-(propionil) piperazin-1-ilo, 4-(3-hidroxipropionil)piperazin-1-ilo, 4-[2-(azetidin-1-il)acetil]piperazin-1-ilo, (R)-3-aminopirrolidin-1-ilo, (S)-3-aminopirrolidin-1-ilo, (3*R*,5*S*)-4-acetil-3,5-dimetilpiperazin-1-ilo, (2*S*,5*R*)-4-acetil-2,5-dimetilpiperazin-1-ilo, (2*RS*,6*SR*)-2,6-dimetilmorfolin-4-il]fenilo, 3-hidroxiazetidin-1-ilo, 3-acetilaminoazetidin-1-ilo, 3-(2-hidroxiacetilamino) azetidin-1-ilo, 3-mesilaminoazetidin-1-ilo, 3-mesiloxiazetidin-ilo, 3-azidoazetidin-1-ilo,3-aminoazetidin-1-ilo,(3*R*)-3-{[(2*S*)-2-hidroxipropanoil] amino}pirrolidin-1-ilo, (3*S*)-3-{[(2*S*)-2-hidroxipropanoil]amino}pirrolidin-1-ilo, (3*S*)-3-(glicoloilamino)pirrolidin-1-ilo y (3*R*)-3-(glicoloilamino) pirrolidin-1-ilo,

R^1 es fluoro, cloro o metilo,

p es 0 o 1,

R^2 se selecciona de hidroxi, amino, azido, metilo, *N*-metilcarbamoilo, *N*,*N*-dimetilcarbamoilo, acetamido, {[(2*S*)-2-hidroxipropanoil]amino}, glicoloilamino, mesilamino, 2-hidroxiacetamido, mesiloxi o *N*-ciclopropilcarbamoilo

q es 0-2, en donde los valores de R^2 pueden ser los mismos o diferentes,

R^3 es 5-fluoro o 5-cloro,

n es 0 o 1,

R^4 es etilo, isopropilo, isobutilo, ciclobutilo o ciclopropilmetilo,

R^5 y R^6 se seleccionan independientemente de hidrogeno, metilo, etilo, metoximetilo, propilo,

o su sal farmaceuticamente aceptable o éster hidrolizable *in vivo*

Por lo tanto, en un aspecto adicional de la invencion, se provee un compuesto de formula (I) (como se describe mas arriba) en donde

Anillo A es un anillo saturado de 4-7 miembros, enlazado a nitrogeno, que contiene opcionalmente un atomo adicional de nitrogeno, oxigeno o azufre, en donde, si anillo A contiene un atomo adicional de nitrogeno, ese nitrógeno puede sustituirse opcionalmente por R^7, en donde

R^3 es halo,

R^4 es C_{1-6}alquilo o carbociclilo, en donde R^4 puede sustituirse de manera opcional en carbono por uno o más R^{14}, en donde

R^5 y R^6 se seleccionan independientemente de hidrogeno o C_{1-6}alquilo, en donde R^5 y R^6, independientemente uno de otro, pueden sustituirse de manera opcional en carbono por uno o mas R^{16},

R^7 se selecciona de C_{1-6}alcanoilo, C_{1-6}alquilsulfonilo, C_{2-6}alquenilsulfonilo, carbociclil-R^{18}- o heterociclil-R^{19}-, en donde R^7 puede sustituirse independientemente de manera opcional en carbono por un grupo seleccionado de R^{20}, y en donde, si dicho heterociclilo contiene una fracción -NH-, ese nitrogeno puede sustituirse opcionalmente por R^{21},

R^{14} es carbociclilo,

R^{16} se selecciona de metoxi,

R^{18} y R^{19} son -C(O)-,

R^{20} se selecciona de halo, ciano, hidroxi, C_{1-6}alcoxi, C_{2-6}alquiniloxi, C_{1-6}alcanoiloxi, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alquil$S(O)_a$, en donde **a** es 2 o heterociclilo, en donde R^{20} puede sustituirse de manera opcional en carbono por uno o más R^{26},

R^{21} es C_{1-6}alquilo,

R^{26} es hidroxi,

p es 0,

q es 0,

n es 0 o 1,

o su sal farmaceuticamente aceptable o éster hidrolizable *in vivo*

Por lo tanto, en un aspecto adicional de la invención, se provee un compuesto de formula (I) (como se describe mas arriba) en donde

Anillo A es un anillo saturado de 6 miembros, enlazado a nitrogeno, que contiene opcionalmente un átomo adicional de nitrogeno, en donde, si anillo A contiene un atomo adicional de nitrogeno, ese nitrógeno puede sustituirse opcionalmente por R^7, en donde

R^7 se selecciona de C_{1-6}alcanoílo, C_{1-6}alquilsulfonílo y C_{2-6}alquenilsulfonílo, en donde R^7 puede sustituirse de manera opcional en carbono por un grupo seleccionado de R^{20}, en donde

R^{20} se selecciona de hidroxi, C_{1-6}alcoxi, C_{1-6}alcanoiloxi y *N,N*-(C_{1-6}alquil)$_2$amino,

p es 0,

q es 0,

R^3 es halo,

n es 0 o 1

R^4 es C_{1-6}alquilo o carbociclilo, en donde R^4 puede sustituirse de manera opcional en carbono por uno o mas R^{14}, en donde

R^{14} es carbociclilo,

R^5 es C_{1-6}alquilo, en donde R^5 puede sustituirse de manera opcional en carbono por uno o mas R^{16}, en donde

R^{16} es metoxi, y

R^6 es hidrogeno,

o su sal farmacéuticamente aceptable o ester hidrolizable *in vivo*

Por lo tanto, en un aspecto adicional de la invencion, se provee un compuesto de fórmula (I) (como se describe mas arriba) en donde

Anillo A es 4-metilsulfonilpiperazin-1-ilo, 4-vinilsulfonilpiperazin-1-ilo, 4-acetilpiperazin-1-ilo, 4-(acetoxiacetil)piperazin-1-ilo, 4-(hidroxiacetil)piperazin-1-ilo, 4-(dimetilaminoacetil)piperazin-1-ilo, 4-(2-dimetilaminoetilsulfonil)piperazin-1-ilo, 4-(2-metoxietilsulfonil)piperazin-1-ilo, 4-(2-hidroxietilsulfonil)piperazin-1-ilo, piperazin-1-ilo o morfolino,

p es 0,

q es 0,

R^3 es halo,

n es 0 o 1,

R^4 es etilo, isopropilo, isobutilo, ciclobutilo o ciclopropilmetilo, R^5 es metilo, etilo, propilo o metoximetilo, y

R^6 es hidrógeno,

o su sal farmaceuticamente aceptable o ester hidrolizable *in vivo*

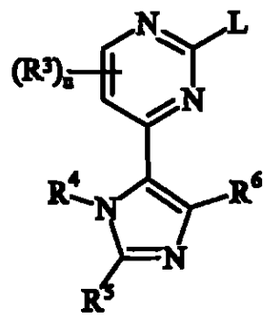
En otro aspecto de la invención, compuestos preferidos de la invencion son cualquiera de los Ejemplos o su sal farmaceuticamente aceptable o ester hidrolizable *in vivo*

En otro aspecto de la invencion, compuestos preferidos de la invencion son uno cualquiera de los Ejemplos 18, 22, 87, 92, 94, 96, 104, 113, 118 o 121, o su sal farmacéuticamente aceptable o ester hidrolizable *in vivo*

Aspectos preferidos de la invencion son aquellos que se refieren al compuesto de formula (I) o su sal farmaceuticamente aceptable

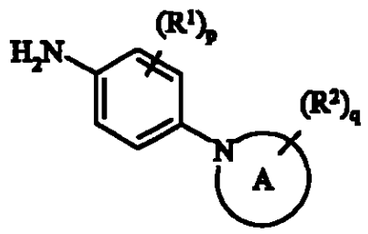
Otro aspecto de la presente invencion provee un proceso para preparar un compuesto de fórmula (I) o su sal farmaceuticamente aceptable o ester hidrolizable *in vivo* proceso que (en donde grupos variables son, a menos que se especifique lo contrario, como se define en formula (I)) consta de

Proceso a) reacción de una pirimidina de formula (II)



(II)

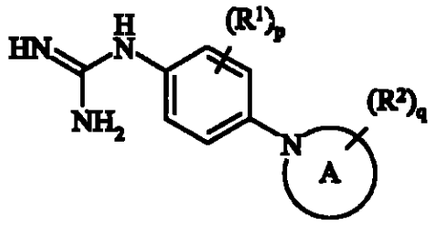
en donde L es un grupo desplazable, con una anilina de fórmula (III)



(III)

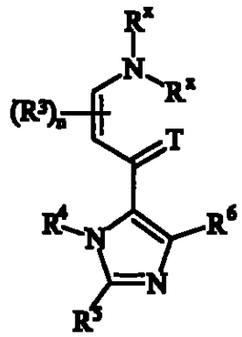
o

Proceso b) hacer reaccionar un compuesto de fórmula (IV)



(IV)

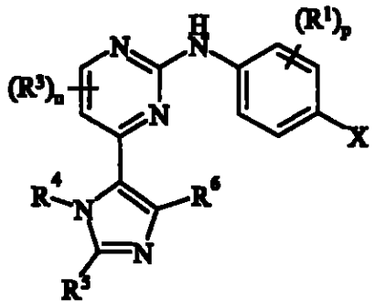
con un compuesto de formula (V)



(V)

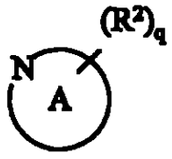
en donde T es O o S, R^x puede ser el mismo o diferente y se selecciona de C_{1-6}alquilo, o

Proceso c) reaccion de una pirimidina de fórmula (VI)



(VI)

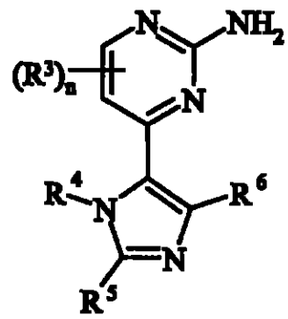
en donde X es un grupo desplazable, con un heterociclilo de formula (VII)



(VII)

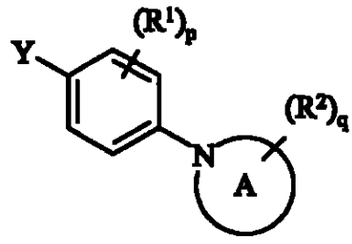
o

Proceso d) para compuestos de formula (I), reacción de una pirimidina de formula (VIII)



(VIII)

con un compuesto de formula (IX)



(IX)

donde Y es un grupo desplazable,

y, posteriormente, si es necesario

i) convertir un compuesto de la formula (I) en otro compuesto de la formula (I),

ii) retirar grupos protectores cualesquiera,

iii) formar una sal farmaceuticamente aceptable o ester hidrolizable *in vivo*

L es un grupo desplazable, valores apropiados de L son, por ejemplo, un grupo halogeno o sulfoniloxi, por ejemplo un grupo cloro, bromo, metanosulfoniloxi o tolueno-4-sulfoniloxi

X es un grupo desplazable, valores apropiados de X son, por ejemplo, un grupo bromo o yodo Preferiblemente X es bromo

Y es un grupo desplazable, valores apropiados de Y son, por ejemplo, un grupo halogeno o sulfoniloxi, por ejemplo un grupo bromo, yodo o trifluorometanosulfoniloxi Preferiblemente Y es yodo

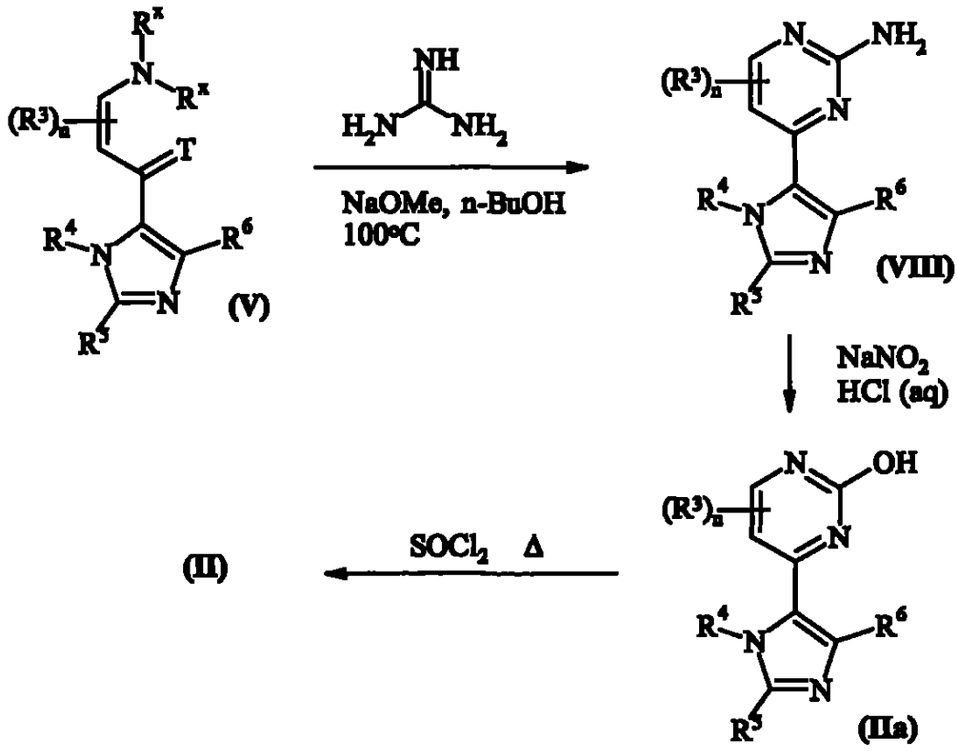
Las condiciones especificas de reacción para lo anterior son las siguientes

Proceso a) Pirimidinas de formula (II) y anilinas de formula (III) pueden hacerse reaccionar conjuntamente

i) en la presencia de un disolvente apropiado, por ejemplo, una cetona tal como acetona o un alcohol tal como etanol o butanol o un hidrocarburo aromático tal como tolueno o *N*-metil pirrolidina, de manera opcional en la presencia de un ácido apropiado, por ejemplo, un ácido inorganico tal como acido clorhidrico o ácido sulfúrico, o un acido organico tal como acido acetico o acido fórmico (o un acido de Lewis apropiado) y a una temperatura en el rango de 0°C a reflujo, preferiblemente reflujo, o

ii) bajo condiciones estandar de Buchwald (por ejemplo, vease *J Am Chem Soc,* **118,** 7215, *J Am Chem Soc,* **119,** 8451, *J Org Chem* **62,** 1568 y 6066) por ejemplo en la presencia de acetato de paladio, en un disolvente adecuado, por ejemplo, un disolvente aromatico tal como tolueno, benceno o xileno, con una base apropiada, por ejemplo una base inorgánica tal como carbonato de cesio o una base orgánica tal como *t*-butoxido de potasio, en la presencia de un ligando apropiado tal como 2,2'-bis(difenilfosfino)-1,1'-binaftilo y a una temperatura en el rango de 25 a 80°C

Pirimidinas de la formula (II) donde L es cloro pueden prepararse de acuerdo con *Esquema 1*

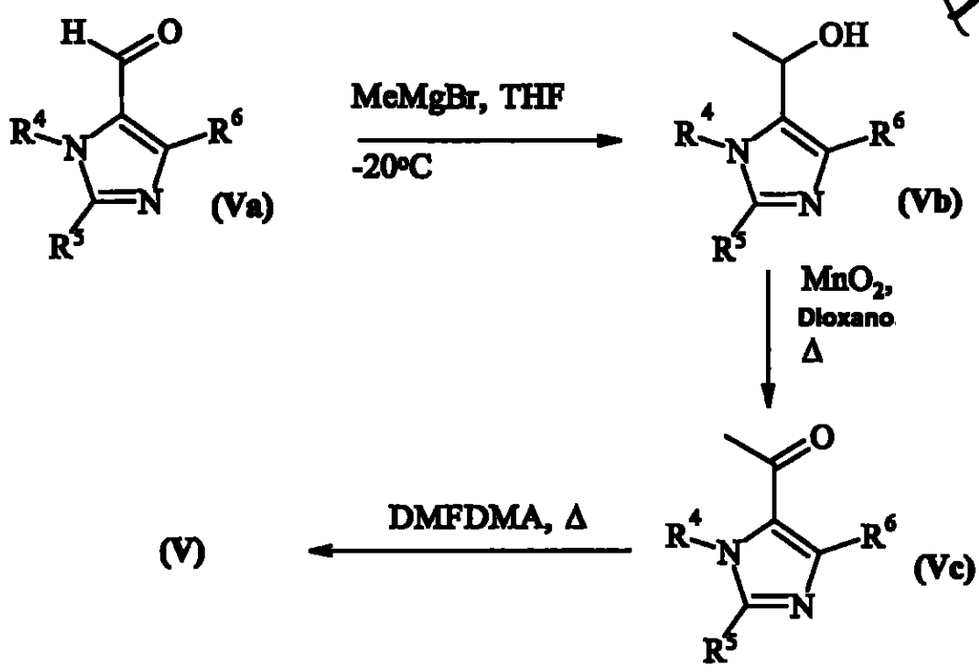


Esquema 1

Anilinas de fórmula (III) son compuestos obtenibles en el comercio, o se conocen en la literatura, o se preparan por procesos estandar conocidos en el arte

Proceso b) Compuestos de formula (IV) y compuestos de formula (V) se hacen reaccionar juntos en un disolvente apropiado tal como *N*-metilpirrolidinona o butanol a una temperatura en el rango de 100-200°C, preferiblemente en el rango de 150-170°C La reaccion se lleva preferiblemente a cabo en la presencia de una base apropiada tal como, por ejemplo, hidruro de sodio, metoxido de sodio o carbonato de potasio

Compuestos de formula (V) pueden prepararse de acuerdo con *Esquema 2*



Esquema 2

Compuestos de formula (IV) y (Va) son compuestos obtenibles en el comercio, o se conocen en la literatura, o se preparan por procesos estándar conocidos en el arte

Proceso c) Compuestos de formula (VI) y aminas de fórmula (VII) pueden hacerse reaccionar juntos bajo condiciones estándar de Buchwald (por ejemplo, véase *J Am Chem Soc* **118**, 7215, *J Am Chem Soc* **119**, 8451, *J Org Chem* **62**, 1568 y 6066) por ejemplo en la presencia de acetato de paladio, en un disolvente adecuado, por ejemplo, un disolvente aromatico tal como tolueno, benceno o xileno, con una base apropiada, por ejemplo una base inorgánica tal como carbonato de cesio o una base organica tal como *t*-butoxido de potasio, en la presencia de un ligando apropiado tal como 2,2'-bis(difenilfosfino)-1,1'-binaftilo y a una temperatura en el rango de 25 a 80°C

Compuestos de formula (VI) pueden prepararse de acuerdo con los procedimientos descritos en WO 02/20512

Heterociclilos de fórmula (VII) son compuestos disponibles en el comercio, o se conocen en la literatura, o pueden prepararse por procesos estandar conocidos en el arte

Proceso d) Compuestos de formula (VIII) y aminas de formula (IX) pueden hacerse reaccionar juntos bajo condiciones estandar de Buchwald como se describe en *Proceso a)*

La sintesis de compuestos de fórmula (VIII) se describe en *Esquema 1*

Compuestos de fórmula (IX) son compuestos obtenibles en el comercio, o se conocen en la literatura, o se preparan por procesos estandar conocidos en el arte

Aminas de formula (VI) son compuestos obtenibles en el comercio, o se conocen en la literatura, o se preparan por procesos estándar conocidos en el arte

Se observará que algunos de los diferentes sustituyentes de anillo en los compuestos de la presente invención pueden introducirse por reacciones estandar de sustitución aromatica o generarse por modificaciones tradicionales de grupo funcional, bien sea antes o inmediatamente despues de los procesos ya mencionados, y como tales se incluyen en el aspecto de los procesos de la invencion Tales reacciones y modificaciones incluyen, por ejemplo, la introducción de un sustituyente por medio de una reaccion de sustitucion aromatica, reduccion de sustituyentes, alquilacion de sustituyentes y oxidacion de sustituyentes Los reactivos y las condiciones de reaccion para tales procedimientos son bien conocidos en el arte quimico Ejemplos de reacciones de sustitución aromatica incluyen la introduccion de un grupo nitro usando acido nitrico concentrado, la introduccion de un grupo acilo usando, por ejemplo, un haluro de acilo y acido de Lewis (tal como tricloruro de aluminio) bajo condiciones de Friedel Crafts, la introduccion de un grupo alquilo usando un haluro de alquilo y acido de Lewis (tal como tricloruro de aluminio) bajo condiciones de Friedel Crafts, y la introducción de un grupo halogeno Ejemplos particulares de modificaciones incluyen la reduccion de un grupo nitro a un

grupo amino mediante por ejemplo, hidrogenacion catalitica con un catalizador de niquel o tratamiento con hierro en la presencia de acido clorhidrico con calentamiento, oxidación de alquiltio a alquilsulfinilo o alquilsulfonilo

Se observara que en algunas de las reacciones mencionadas aqui puede ser necesario/deseable proteger grupos sensibles cualesquiera en los compuestos Los casos en donde la protección es necesaria o deseable y los métodos apropiados de proteccion son conocidos por los expertos en el arte Pueden usarse grupos protectores tradicionales de acuerdo con la practica estandar (para ilustración, véase T W Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991) En consecuencia, si los reactivos incluyen grupos tales como amino, carboxi o hidroxi, puede ser deseable proteger el grupo en algunas de las reacciones mencionadas aqui

Un grupo protector apropiado para un grupo amino o alquilamino es, por ejemplo, un grupo acilo, por ejemplo un grupo alcanoilo tal como un acetilo, un grupo alcoxicarbonilo, por ejemplo un grupo metoxicarbonilo, etoxicarbonilo o *t*-butoxicarbonilo, un grupo arilmetoxicarbonilo, por ejemplo benciloxicarbonilo, o un grupo aroilo, por ejemplo benzoilo Las condiciones de desproteccion para los grupos protectores anteriores varian necesariamente con la eleccion del grupo protector Asi, por ejemplo, un grupo acilo tal como un grupo alcanoilo o alcoxicarbonilo o un grupo aroilo pueden retirarse por ejemplo, mediante hidrolisis con una base apropiada tal como un hidroxido de metal alcalino, por ejemplo hidróxido de litio o sodio Alternativamente puede retirarse un grupo acilo tal como un grupo *t*-butoxicarbonilo, por ejemplo, mediante tratamiento con un ácido apropiado tal como acido clorhidrico, sulfurico o fosforico o acido trifluoroacetico y un grupo arilmetoxicarbonilo tal como un grupo benciloxicarbonilo puede retirarse, por ejemplo, mediante hidrogenacion sobre un catalizador tal como paladio sobre carbono, o mediante el tratamiento con un ácido de Lewis por ejemplo tris(trifluoroacetato) de boro Un grupo protector alternativo apropiado para un grupo amino primario es, por ejemplo, un

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grupo ftaloilo que puede retirarse mediante tratamiento con una alquilamina, por ejemplo dimetilaminopropilamina, o con hidrazina

Un grupo protector apropiado para un grupo hidroxi es, por ejemplo, un grupo acilo, por ejemplo un grupo alcanoilo tal como acetilo, un grupo aroilo, por ejemplo benzoilo, o un grupo arilmetilo, por ejemplo bencilo Las condiciones de desproteccion para los grupos protectores mencionados variaran necesariamente con la elección del grupo protector Asi, por ejemplo, un grupo acilo tal como un alcanoilo o un grupo aroilo pueden retirarse, por ejemplo, mediante hidrolisis con una base apropiada tal como un hidroxido de metal alcalino, por ejemplo hidroxido de litio o sodio Alternativamente puede retirarse un grupo arilmetilo tal como un grupo bencilo, por ejemplo, mediante hidrogenacion sobre un catalizador tal como paladio sobre carbono

Un grupo protector apropiado para un grupo carboxi es, por ejemplo, un grupo esterificante, por ejemplo un grupo metilo o etilo que puede retirarse, por ejemplo, por hidrólisis con una base tal como hidróxido de sodio, o por ejemplo un grupo *t*-butilo que puede retirarse, por ejemplo, por tratamiento con un ácido, por ejemplo un ácido orgánico tal como acido trifluoroacético, o por ejemplo un grupo bencilo que puede retirarse, por ejemplo, por hidrogenación sobre un catalizador tal como paladio sobre carbono

Los grupos protectores pueden retirarse en cualquier fase conveniente en la sintesis usando tecnicas tradicionales bien conocidas en el arte quimico

Como se declaro mas arriba en el texto, los compuestos definidos en la presente invencion poseen actividad antiproliferación celular tal como actividad antineoplasica que se cree que resulta de la actividad inhibidora CDK del compuesto Estas propiedades pueden evaluarse, por ejemplo, usando los procedimientos expuestos más adelante

Analisis

Se han usado las siguientes abreviaturas

HEPES es acido *N*-[2-hidroxietil]piperazin-*N* -[2-etanosulfonico]

DTT es ditiotreitol

PMSF es fluoruro de fenilmetilsulfonilo

Los compuestos se probaron en un analisis de cinasa *in vitro* en un formato de 96 pocillos empleando el Ensayo de Proximidad con Escintilacion (SPA obtenido de Amersham) para medir la incorporación de [γ-33-P]-Adenosina Trifosfato en un sustrato de prueba (GST-proteina de Retinoblastoma, GST- Rb) En cada pocillo se deposito el compuesto a probarse (diluido en DMSO y agua para corregir las concentraciones) y en pocillos de control o bien roscovitina como control de inhibidor o bien DMSO como control positivo

Aproximadamente 0 2µl de enzima parcialmente purificada de CDK2/Ciclina E (cantidad dependiente de la actividad enzimática), diluidos en 25µl de tampon de incubación, se agregaron a cada pocillo, luego 20µl de mezcla GST-Rb/ATP/ATP33 (que contenia 0 5µg GST-Rb y 0 2µM ATP y 0 14µCi [γ-33-P]-Adenosina Trifosfato en tampon de incubacion), y la mezcla resultante se agito suavemente, a continuacion se incubo a temperatura de la sala por 60 minutos

A cada pocillo se agregaron entonces 150µl de solucion de detencion (***"stop solution"***) que contenia (0 8mg/pocillo de microgranulo de Proteina A-PVT SPA (Amersham)), 20pM/pocillo de Anti-Glutatión Transferasa, IgG de conejo (obtenida de Molecular Probes), 61mM EDTA y 50mM HEPES pH 7 5 que contenia 0 05% de azida de sodio

Las placas se sellaron con selladores de placas Topseal-S, se dejaron durante dos horas y luego se rotaron a 2500rpm, 1124xg , por 5 minutos Las placas se leyeron en un Topcount durante 30 segundos por pocillo

El tampon de incubación usado para diluir la enzima y las mezclas de sustrato contenia 50mM HEPES pH7 5, 10mM $MnCl_2$, 1mM DTT, 100µM de vanadato de sodio, 100µM NaF, 10mM de glicerofosfato de sodio, BSA (1mg/ml final)

Sustrato de Prueba

En este analisis tan solo se empleo una parte de la proteina de retinoblastoma (Science 1987 Mar13, 235 (4794) 1394-1399, Lee W H, Bookstein R, Hong F, Young L J, Shew J Y, Lee E Y), fusionada a un marcador GST Se realizó PCR del gen de retinoblastoma que codifica los aminoacidos 379-928 (obtenidos del plasmido de retinoblastoma ATCC pLRbRNL), y la secuencia se clonó en el vector de fusion pGEx 2T (Smith D B and Johnson, K.S Gene 67, 31 (1988), que contenia un promotor tac de expresión inducible, gen lac I^q interno para uso en cualquier anfitrión de *E coli*, y una region codificadora de segmentacion de trombina – obtenida de Pharmacia Biotech), que se utilizo para amplificar los aminoacidos 792-928 Esta secuencia se clono nuevamente en pGEx 2T

La secuencia 792-928 de retinoblastoma asi obtenida se expreso en *E coli* (celulas BL21 (DE3) pLysS) usando tecnicas estándar de expresion inducible, y se purificó en la siguiente forma

Pasta de *E coli* se resuspendió en 10ml/g de tampon NETN (50mM Tris pH 7 5, 120mM NaCl, 1mM EDTA, 0 5% v/v NP-40, 1mM PMSF, 1ug/ml leupeptina, 1ug/ml aprotinina y 1ug/ml pepstatina) y se sometió a sonicación por 2 x 45 segundos por 100ml homogenato Luego de la centrifugación, el sobrenadante se cargo en una columna de glutation sefarosa de 10ml (Pharmacia Biotech, Herts, UK), y se lavó con tampon NETN Luego de lavar con tampón de cinasa (50mM HEPES pH 7 5, 10mM $MgCl_2$, 1mM DTT, 1mM PMSF, 1ug/ml leupeptina, 1ug/ml aprotinina y 1ug/ml pepstatina), la proteina se eluyo con 50mM de glutation reducido en tampon de cinasa Las fracciones que contenian GST-Rb (792-927) se agruparon y se dializaron de un dia para otro contra el tampon de cinasa El producto final se analizo por Dodeca Sulfato de Sodio (SDS) PAGE (gel de poliacilamida) usando geles 8-16% Tris-Glicina (Novex, San Diego, USA)

CDK2 y Ciclina E

Los marcos de lectura abiertos de CDK2 y Ciclina E se aislaron por PCR de transcriptasa reversa usando una célula HeLa y mARN de linfocito

T activado como plantilla y se clonaron en el vector de expresión de insecto pVL1393 (obtenido de Invitrogen 1995 catalogo numero V1392-20) CDK2 y Ciclina E se expresaron entonces de manera dual [usando una técnica estandar de co-infección con virus Baculogold] en el sistema celular SF21 de insecto (células de Spodoptera Frugiperda derivadas de tejido ovarico de la Oruga Militar Tardia (***"Fall Army Worm"***) - disponible en el comercio)

Ejemplo de Produccion de Ciclina E/CDK2

El siguiente Ejemplo proporciona detalles de la produccion de Ciclina E/CDK2 en celulas SF21 (en TC100 + 10% FBS(TCS) + 0 2% Pluronic) con infeccion dual MOI 3 para cada virus de Ciclina E & CDK2

Células SF21 cultivadas en tubos de cara plana sobre la que se fija el cultivo (***"roller bottles"***) con 2 33 x 10^6 células/ml se usaron para inocular 10 x 500 ml de tubos de cara plana con 0 2 x 10E6 células/ml Los tubos de cara plana se incubaron en un equipo de tubos de cara plana (***"a roller rig"***) a 28°C

Después de 3 días (72 horas) se contaron las células, y se encontro que el promedio de 2 tubos era 1 86 x 10E6 células/ml (99% viables) Los cultivos se infectaron entonces con los virus duales con una MOI-3 por cada virus

Los virus se mezclaron entre si antes de la adicion a los cultivos, y los cultivos se regresaron al equipo de los tubos de cara plana a 28°C

Despues de 2 dias (48 horas) pos-infeccion se recogieron los 5 litros de cultivo El conteo total de células al momento de la recoleccion fue de 1 58 x 10E6 células/ml (99% viables) Las celulas se rotaron a 2 500 rpm, 30 minutos, 4°C en Heraeus Omnifuge 2 0 RS en lotes de 250 ml El sobrenadante se descarto

Co-Purificación Parcial de Cdk2 y Ciclina E

Celulas Sf21 se resuspendieron en tampon de lisis (50mM Tris pH 8 2, 10mM $MgCl_2$, 1mM DTT, 10mM glicerofosfato, 0 1mM ortovanadato de sodio, 0 1mM NaF, 1mM PMSF, 1ug/ml leupeptina y 1ug/ml aprotinina)

y se homogeneizaron por 2 minutos en un homogeneizador Dounce de 10ml Luego de la centrifugacion, el sobrenadante se cargo en una columna de intercambio iónico Poros HQ/M 1 4/100 (PE Biosystems, Hertford, Reino Unido) Cdk2 y Ciclina E se co-eluyeron al comienzo de una gradiente 0-1M NaCl (efectuada en tampon de lisis menos inhibidores de proteasa) sobre 20 volumenes de columna La co-elucion se verifico mediante tecnica de transferencia *Western blot* usando anticuerpos anti-Cdk2 y anti-Ciclina E (Santa Cruz Biotechnology, California, US)

Por analogía, pueden construirse analisis diseñados para evaluar la inhibicion de CDK1 y CDK4 CDK2 (EMBL - Laboratorio Europeo de Biologia Molecular (European Molecular Biology Laboratory) Acceso No X62071) puede usarse conjuntamente con Ciclina A o Ciclina E (véase EMBL Acceso No M73812), y mayores detalles para tales analisis se incluyen en la Publicación Internacional PCT No WO99/21845, cuyas secciones relevantes de Evaluacion Biológica & Bioquimica se incorporan aqui por referencia

Aunque las propiedades farmacológicas de los compuestos de la formula (I) varian con el cambio estructural, en general la actividad que poseen los compuestos de la fórmula (I) puede demostrarse en concentraciones IC_{50} o dosis en el rango de 250μM a 1nM

Cuando se prueban en el análisis *in vitro* ya mencionado, la actividad inhibidora de CDK2 de Ejemplo 8 se midio como IC_{50}= 0 181μM

La actividad *in vivo* de los compuestos de la presente invencion puede evaluarse por técnicas estándar, por ejemplo midiendo la inhibicion del crecimiento celular y evaluando la citotoxicidad

La inhibición del crecimiento celular puede medirse tiñendo las celulas con sulforrodamina B (SRB), un tinte fluorescente que tiñe proteinas y, por lo tanto, proporciona un estimativo de la cantidad de proteina (es decir, celulas) en un pocillo (vease Boyd, M R (1989) Status of the NCI preclinical antitumour drug discovery screen Prin Prac Oncol 10 1-12) Por consiguiente, se aportan los siguientes detalles de medir la inhibicion del crecimiento celular

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Las celulas se depositaron en placas de 96 pocillos en medio apropiado en un volumen de 100ml, el medio era Medio MEM modificado por Dulbeco (DMEM) para MCF-7, SK-UT-1B y SK-UT-1 Se permitio a las celulas adherirse de un dia para otro, a continuacion se agregaron compuestos inhibidores en varias concentraciones en una concentracion maxima de 1% DMSO (v/v) Se analizo una placa de control para obtener un valor de las celulas antes de la dosificación Las células se incubaron a 37°C, (5% CO_2) durante tres dias

Al final de los tres dias se agrego TCA a las placas a una concentracion final de 16% (v/v) Luego se incubaron las placas a 4°C durante 1 hora, se retiro el sobrenadante y se lavaron las placas en agua de la llave Luego de secar, se agregaron 100ml de tinte SRB (0 4% SRB en 1% de acido acético) durante 30 minutos a 37°C Se retiro el exceso de SRB y las placas se lavaron en 1% de ácido acético

El SRB ligado a proteina se solubilizó en 10mM Tris pH7 5 y se agito durante 30 minutos a temperatura de la sala Los ODs se leyeron a 540nm, y se determinó la concentracion de inhibidor que producia 50% de inhibicion del crecimiento de un trazado semi-logaritmico de la concentracion del inhibidor versus absorbencia La concentracion de compuesto que redujo la densidad óptica por debajo de la obtenida cuando las celulas se depositaron sobre las placas al inicio del experimento produjo el valor de la toxicidad

Valores IC_{50} tipicos para los compuestos de la invencion, cuando se prueban en el análisis SRB, están en el rango 1mM a 1nM

De acuerdo con un aspecto adicional de la invencion se provee una composición farmacéutica que comprende un derivado de pirimidina de la formula (I), o una sal farmacéuticamente aceptable o su éster hidrolizable *in vivo*, como se define más arriba en el texto en asociación con un diluyente o vehiculo farmaceuticamente aceptable

La composicion puede estar en una forma apropiada para administracion oral, por ejemplo como una tableta o capsula, para inyeccion parenteral (incluida intravenosa, subcutánea, intramuscular, intravascular o

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infusion) como una solucion estérilo, suspension o emulsion, para administracion local como un ungüento o crema para administracion rectal tal como un supositorio

En general, las composiciones anteriores pueden prepararse en una forma tradicional usando excipientes tradicionales

El compuesto de formula (I) se administrará normalmente a un animal de sangre caliente en una dosis unitaria en el rango 5-5000 mg por m^2 de area corporal del animal, es decir, aproximadamente 0 1-100 mg/kg, y esto normalmente proporciona una dosis terapeuticamente efectiva Una forma de dosis unitaria tal como una tableta o cápsula contendra usualmente, por ejemplo 1-250 mg de ingrediente activo Preferiblemente se emplea una dosis diaria en el rango de 1-50 mg/kg No obstante, la dosis diaria variara necesariamente dependiendo del anfitrion tratado, la via particular de administracion, y la gravedad de la enfermedad que se esta tratando En consecuencia, la dosificación óptima puede determinarse por el profesional medico que esta tratando a cualquier paciente particular

De acuerdo con un aspecto adicional de la presente invencion se provee un compuesto de la fórmula (I), o una sal farmaceuticamente aceptable o su éster hidrolizable *in vivo*, como se define mas arriba en el texto para uso en un metodo de tratamiento del cuerpo humano o animal mediante terapia

Hemos descubierto que los compuestos definidos en la presente invencion, o una sal farmaceuticamente aceptable o su ester hidrolizable *in vivo*, son inhibidores efectivos del ciclo celular (agentes de antiproliferación celular), propiedad que se cree que se deriva de sus propiedades inhibidoras CDK En consecuencia, se espera que los compuestos de la presente invencion sean utiles en el tratamiento de enfermedades o afecciones mediadas solas o en parte por enzimas CDK, es decir, los compuestos pueden usarse para producir un efecto inhibidor CDK en un animal de sangre caliente necesitado de tal tratamiento Asi, los compuestos de la presente invención proveen un metodo para tratar la proliferacion de celulas cancerosas caracterizado por la inhibicion de las enzimas CDK, es decir, los

compuestos pueden usarse para producir un efecto antiproliferativo mediado solo o en parte por la inhibición CDKs Se espera que tal compuesto de la invencion posea un amplio rango de propiedades antineoplasicas puesto que las CDKs han sido implicadas en muchos canceres humanos comunes tales como leucemia y cáncer de mama, pulmon, colon, recto, estómago, prostata, vejiga, pancreas y ovarios Por consiguiente, se espera que un compuesto de la invencion posea actividad antineoplasica contra estos canceres Se espera además que un compuesto de la presente invencion posea actividad contra un rango de leucemias, canceres linfoides y tumores solidos tales como carcinomas y sarcomas en tejidos tales como el higado, riñón, próstata y páncreas En particular, se espera que tales compuestos de la invencion retrasen ventajosamente el crecimiento de tumores sólidos primarios y recurrentes de, por ejemplo, el colon, mama, prostata, pulmones y piel Mas particularmente, se espera que tales compuestos de la invención, o una sal farmaceuticamente aceptable o su ester hidrolizable *in vivo*, inhiban el crecimiento de aquellos tumores solidos primarios y recurrentes que se asocian con CDKs, especialmente aquellos tumores que son significativamente dependientes de CDKs para su crecimiento y difusión, incluidos, por ejemplo, ciertos tumores del colon, mama, prostata, pulmón, vulva y piel

Cuando se alude al cáncer en la presente solicitud, en particular este se refiere a leucemia, cancer de mama, cancer de pulmon, cancer de colon, cancer rectal, cancer del estomago, cancer de prostata, cáncer de vejiga, cancer del pancreas, cancer de ovarios, cáncer del higado, cancer del riñon, cáncer de piel y cáncer de la vulva

Se espera además que un compuesto de la presente invencion poseera actividad contra las otras enfermedades de proliferacion celular en un amplio rango de otros estados patológicos incluidas leucemias, trastornos fibroproliferativos y diferenciativos, psoriasis, artritis reumatoide, sarcom de Kaposi, hemangioma, nefropatias agudas y cronicas, ateroma, aterosclerosis, restenosis arterial, enfermedades autoinmunitarias,

inflamación aguda y cronica, enfermedades oseas y enfermedades oculares con proliferacion vascular retiniana

Asi, de acuerdo con este aspecto de la invencion se provee un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable o su ester hidrolizable *in vivo*, como se define más arriba en el texto para uso como un medicamento, y el uso de un compuesto de la formula (I), o una sal farmacéuticamente aceptable o su ester hidrolizable *in vivo*, como se define más arriba en el texto en la manufactura de un medicamento para uso en la produccion de un efecto inhibidor del ciclo celular (antiproliferacion celular) en un animal de sangre caliente tal como el hombre Particularmente, se produce un efecto inhibidor evitando la entrada en o la progresión a través de la fase S mediante la inhibicion de CDK2, CDK4 y/o CDK6, especialmente CDK2, y la fase M mediante inhibicion de CDK1

De acuerdo con una caracteristica adicional de la invencion, se provee un compuesto de la formula (I), o una sal farmaceuticamente aceptable o su ester hidrolizable *in vivo*, como se define mas arriba en el texto en la manufactura de un medicamento para uso en el tratamiento de canceres (tumores solidos y leucemias), trastornos fibroproliferativos y diferenciativos, psoriasis, artritis reumatoide, sarcoma de Kaposi, hemangioma, neuropatias agudas y crónicas, ateroma, aterosclerosis, restenosis arterial, enfermedades autoinmunitarias, inflamacion aguda y cronica, enfermedades oseas y enfermedades oculares con proliferación vascular retiniana, particularmente en el tratamiento de neoplasias malignas

De acuerdo con una caracteristica adicional de la invencion, se contempla el uso de un compuesto de la formula (I), o su sal farmaceuticamente aceptable o éster hidrolizable *in vivo*, como se define más arriba en el texto en la fabricacion de un medicamento para uso en el tratamiento del cancer

De acuerdo con una caracteristica adicional de la invencion, se contempla el uso de un compuesto de la fórmula (I), o su sal farmaceuticamente aceptable o ester hidrolizable *in vivo*, como se define

más arriba en el texto en la fabricacion de un medicamento para uso en la produccion de un efecto inhibidor de CDK

De acuerdo con una caracteristica adicional de este aspecto de la invencion se provee un metodo para producir un efecto inhibidor del ciclo celular (antiproliferación celular) 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 compuesto como se define inmediatamente mas arriba Particularmente, se produce un efecto inhibidor evitando la entrada en o la progresion a traves de la fase S mediante la inhibicion de CDK2 y CDK4, especialmente CDK2, y la fase M mediante inhibición de CDK1

De acuerdo con una caracteristica mas de este aspecto de la invencion se provee un metodo para producir un efecto inhibidor del ciclo celular (antiproliferación celular) 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 compuesto de formula (I) o una sal farmaceuticamente aceptable o su ester hidrolizable *in vivo* como se define más arriba en el texto Particularmente, se produce un efecto inhibidor evitando la entrada en o la progresión a traves de la fase S mediante la inhibición de CDK2 y CDK4, especialmente CDK2, y la fase M mediante inhibición de CDKI

De acuerdo con una caracteristica adicional de este aspecto de la invención se provee un método de tratar canceres (tumores solidos y leucemias), trastornos fibroproliferativos y diferenciativos, psoriasis, artritis reumatoide, sarcoma de Kaposi, hemangioma, neuropatias agudas y cronicas, ateroma, aterosclerosis, restenosis arterial, enfermedades autoinmunitarias, inflamacion aguda y cronica, enfermedades óseas y enfermedades oculares con proliferacion vascular retiniana, 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 compuesto de fórmula (I) o una sal farmacéuticamente aceptable o su ester hidrolizable *in vivo* como se define más arriba en el texto

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Particularmente se provee un método de tratar cáncer 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 compuesto de formula (I) o una sal farmacéuticamente aceptable o su ester hidrolizable *in vivo* como se define más arriba en el texto

Se contempla particularmente un metodo de producir un efecto inhibidor de CDK 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 compuesto de formula (I) o una sal farmaceuticamente aceptable o su ester hidrolizable *in vivo* como se define mas arriba en el texto

En un aspecto adicional de la invencion se provee una composición farmacéutica que comprende un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable o su ester hidrolizable *in vivo*, como se define mas arriba en el texto en asociacion con un diluyente o vehículo farmaceuticamente aceptable para uso en la produccion de un efecto inhibidor del ciclo celular (antiproliferación celular) en un animal de sangre caliente tal como el hombre

En un aspecto adicional de la invencion se provee una composicion farmaceutica que comprende un compuesto de la formula (I), o una sal farmaceuticamente aceptable o su éster hidrolizable *in vivo*, como se define mas arriba en el texto en asociación con un diluyente o vehiculo farmaceuticamente aceptable para uso en el tratamiento de canceres (tumores solidos y leucemias), trastornos fibroproliferativos y diferenciativos, psoriasis, artritis reumatoide, sarcoma de Kaposi, hemangioma, neuropatias agudas y cronicas, ateroma, aterosclerosis, restenosis arterial, enfermedades autoinmunitarias, inflamacion aguda y crónica, enfermedades óseas y enfermedades oculares con proliferacion vascular retiniana, en un animal de sangre caliente tal como el hombre

En un aspecto adicional de la invención se provee una composicion farmaceutica que comprende un compuesto de la formula (I), o una sal farmaceuticamente aceptable o su ester hidrolizable *in vivo*, como se define

anteriormente en el texto en asociación con un diluyente o vehiculo farmaceuticamente aceptable para uso en el tratamiento de cancer en un animal de sangre caliente tal como el hombre

En un aspecto adicional de la invención se provee una composicion farmaceutica que comprende un compuesto de la formula (I), o una sal farmaceuticamente aceptable o su ester hidrolizable *in vivo*, como se define anteriormente en el texto en asociación con un diluyente o vehiculo farmaceuticamente aceptable para uso en la producción de un efecto inhibidor de CDK en un animal de sangre caliente tal como el hombre

Evitar el ingreso de las celulas en la síntesis de ADN mediante la inhibición de actividades esenciales que inician la fase S tal como la iniciacion de CDK2 puede ser igualmente util en proteger las celulas normales del cuerpo de la toxicidad de agentes farmaceuticos especificos del ciclo La inhibicion de CDK2 o 4 evitará la progresion al ciclo celular en células normales, que podria limitar la toxicidad de agentes farmaceuticos especificos del ciclo celular, los cuales actuan en la fase S, G2 o mitosis Tal proteccion puede traducirse en la prevención de la perdida de cabello, asociada normalmente con estos agentes

Por lo tanto, en un aspecto adicional de la invencion se provee un compuesto de fórmula (I) como se define mas arriba, o una sal farmacéuticamente aceptable o su éster hidrolizable *in vivo* para uso como un agente de proteccion celular

Por lo tanto, en un aspecto adicional de la invencion se provee un compuesto de fórmula (I) como se define más arriba, o una sal farmaceuticamente aceptable o su éster hidrolizable *in vivo* para uso en evitar la perdida del cabello, resultante del tratamiento de neoplasias malignas con agentes farmacéuticos

Ejemplos de agentes farmaceuticos para tratar neoplasias malignas que, como se sabe, ocasionan la perdida del cabello, incluyen agentes alquilantes tales como ifosfamida y ciclofosfamida, antimetabolitos tales como metotrexato, 5-fluorouracilo, gemcitabina y citarabina, antineoplasicos análogos tales como vincristina, vinblastina, vindesina,

vinorelbina, taxanos tales como paclitaxel y docetaxel, inhibidores de topoisomerasa I tales como irinotecano y topotecano, antibioticos citotóxicos tales como doxorubicina, daunorubicina, mitoxantrona, actinomicina-D y mitomicina, y otros tales como etoposido y tretinoina

En otro aspecto de la invención, el compuesto de formula (I), o una sal farmaceuticamente aceptable o su éster hidrolizable *in vivo*, puede administrarse en asociacion con uno o mas de los anteriores agentes farmaceuticos En este caso el compuesto de formula (I) puede administrarse por medios sistémicos o no sistemicos Particularmente, el compuesto de fórmula (I) puede administrarse por medios no sistemicos, por ejemplo administracion local

Por lo tanto, en una característica adicional de la invención, se provee un metodo de prevenir la pérdida del cabello durante el tratamiento para una o más neoplasias malignas con agentes farmacéuticos, en un animal de sangre caliente, tal como el hombre, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de formula (I), o una sal farmaceuticamente aceptable o su ester hidrolizable *in vivo*

En una característica adicional de la invención, se provee un método de prevenir la perdida del cabello durante el tratamiento para una o mas neoplasias malignas con agentes farmaceuticos, en un animal de sangre caliente, tal como el hombre, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I), o una sal farmaceuticamente aceptable o su éster hidrolizable *in vivo* en administración simultánea, secuencial o separada con una cantidad efectiva de dicho agente farmaceutico

De acuerdo con un aspecto adicional de la invencion se provee una composicion farmacéutica para uso en prevenir la pérdida del cabello resultante del tratamiento de neoplasias malignas con agentes farmaceuticos, que comprende un compuesto de fórmula (I), o una sal farmacéuticamente aceptable o su éster hidrolizable *in vivo*, y dicho agente farmacéutico, en asociación con un diluyente o vehiculo farmaceuticamente aceptable

De acuerdo con un aspecto adicional de la presente invencion se provee un botiquin que comprende un compuesto de formula (I), o una sal farmacéuticamente aceptable o su éster hidrolizable *in vivo*, y un agente farmaceutico para tratar neoplasias malignas conocido por causar la perdida del cabello

De acuerdo con un aspecto adicional de la presente invencion se provee un botiquin que comprende

a) un compuesto de formula (I), o una sal farmaceuticamente aceptable o su ester hidrolizable *in vivo*, en una primera formulación unitaria,

b) un agente farmaceutico para tratar neoplasias malignas que se conoce por causar la perdida del cabello, en una segunda formulacion unitaria, y

c) medios de envase para contener dichas formulaciones primera y segunda

De acuerdo con otra caracteristica de la invencion se provee el uso de un compuesto de la formula (I), o una sal farmacéuticamente aceptable o su éster hidrolizable *in vivo*, en la manufactura de un medicamento para la prevencion de la perdida del cabello durante el tratamiento de neoplasias malignas con agentes farmacéuticos

De acuerdo con un aspecto adicional de la presente invencion se provee un tratamiento de combinacion para la prevención de la perdida del cabello, que comprende la administracion de una cantidad efectiva de un compuesto de la formula (I), o una sal farmaceuticamente aceptable o su ester hidrolizable *in vivo*, de manera opcional conjuntamente con un diluyente o vehiculo farmacéuticamente aceptable, con la administracion simultanea, secuencial o separada de una cantidad efectiva de un agente farmaceutico para el tratamiento de neoplasias malignas a un animal de sangre caliente, tal como el hombre

Como se manifesto mas arriba, el tamaño de la dosis requerida para el tratamiento terapeutico o profilactico de una particular enfermedad de proliferacion celular variará necesariamente dependiendo del anfitrion tratado, la via de administración y la gravedad de la afeccion que se está

tratando Se preve una dosis unitaria en el rango, por ejemplo, 1-100 mg/kg, preferiblemente 1-50 mg/kg

La actividad inhibidora CDK, definida mas arriba en el texto, puede aplicarse como terapia unica o puede incluir, ademas de un compuesto de la invención, una o mas de otras sustancias y/o tratamientos Tal tratamiento conjunto puede lograrse mediante la administración simultanea, secuencial o separada de los componentes individuales del tratamiento En el campo de la oncologia médica es una práctica normal emplear una combinación de diferentes formas de tratamiento para tratar cada paciente con cancer En la oncologia medica, el otro (los otros) componente(s) de tal tratamiento conjunto, aparte del tratamiento inhibidor del ciclo celular definido mas arriba en el texto puede ser cirugia, radioterapia o quimioterapia Tal quimioterapia puede cubrir las principales categorias de agente terapeutico

(i) otros agentes inhibidores del ciclo celular que operan por los mismos o diferentes mecanismos de los definidos más arriba en el texto,

(ii) agentes citostaticos tales como antiestrgenos (por ejemplo tamoxifeno, toremifeno, raloxifeno, droloxifeno, yodoxifeno), progestogenos (por ejemplo megestrol acetato), inhibidores de aromatasa (por ejemplo anastrozol, letrazol, vorazol, exemestano), antiprogestogenos, antiandrogenos (por ejemplo flutamida, nilutamida, bicalutamida, acetato de ciproterona), agonistas LHRH y antagonistas (por ejemplo acetato de goserelina, leuprolida), inhibidores de testosterona 5α-dihidroreductasa (por ejemplo finasteride), agentes anti-invasivos (por ejemplo inhibidores de metaloproteinasa como marimastat e inhibidores de la funcion de receptor de activador del plasminógeno tipo urocinasa) e inhibidores de la funcion de factor de crecimiento, (tales factores de crecimiento incluyen por ejemplo factor de crecimiento derivado de plaquetas y factor de crecimiento de hepatocitos, tales inhibidores incluyen anticuerpos de factor de crecimiento, anticuerpos de receptor de factor de crecimiento, inhibidores de tirosina cinasa e inhibidores de serina/treonina cinasa), y

(iii) medicamentos antiproliferativos/antineoplasicos y sus combinaciones, como se usan en la oncologia medica, tales como

antimetabolitos (por ejemplo antifolatos como metotrexato, fluoropirimidinas como 5-fluorouracilo, análogos de purina y adenosina, citarabina), antibioticos antineoplasicos (por ejemplo antraciclinas como doxorubicina, daunomicina, epirubicina e idarubicina, mitomicina-C, dactinomicina, mitramicina), derivados de platino (por ejemplo cisplatino, carboplatino), agentes alquilantes (por ejemplo mostaza nitrogenada, melfalan, clorambucilo, busulfan, ciclofosfamida, ifosfamida, nitrosoureas, tiotepa), agentes antimitóticos (por ejemplo antineoplasicos como vincristina y taxoides como taxol, taxotere), inhibidores de topoisomerasa (por ejemplo epipodofilotoxinas como etopósido y teniposido, amsacrina, topotecan) De acuerdo con este aspecto de la invencion se provee un producto farmacéutico que comprende un compuesto de la formula (I) como se define más arriba en el texto y una sustancia adicional antineoplásica como se define mas arriba en el texto para el tratamiento conjunto del cancer

Aparte de su empleo en medicina terapeutica, los compuestos de formula (I) y sus sales farmacéuticamente aceptables son igualmente utiles como herramientas farmacológicas en el desarrollo y estandarización de sistemas de prueba *in vitro* e *in vivo* para la evaluacion de los efectos de inhibidores de la actividad del ciclo celular en animales de laboratorio tales como gatos, perros, conejos, monos, ratas y ratones, como parte de la investigación de nuevos agentes terapeuticos

En las demas caracteristicas anteriores de composicion farmaceutica, proceso, metodo, empleo y manufactura del medicamento, se aplican igualmente las incorporaciones alternativas y preferidas de los compuestos de la invencion descritas aqui

Ejemplos

La invención se ilustrará ahora mediante los siguientes ejemplos no limitantes en los cuales, a menos que se especifique lo contrario

(i) las temperaturas se dan en grados Celsius (°C), las operaciones se llevaron a cabo a temperatura de la sala o a temperatura ambiente, es decir, a una temperatura en el rango de 18-25°C,

(ii) las soluciones organicas se secaron sobre sulfato de magnesio anhidro, la evaporacion del disolvente se llevo a cabo usando un evaporador rotatorio bajo presion reducida (600-4000 Pascals, 4 5-30mmHg) con una temperatura de baño de hasta 60°C,

(iii) cromatografía significa cromatografía de destello en gel de silice, la cromatografía de capa fina (TLC) se llevó a cabo en placas de gel de silice,

(iv) en general, el curso de las reacciones se siguio por TLC y los tiempos de reaccion se dan con fines de ilustracion unicamente,

(v) los productos finales tuvieron espectros satisfactorios de resonancia magnetica nuclear protonica (NMR) y/o datos de espectros de masas,

(vi) los rendimientos se dan para ilustracion unicamente y no son necesariamente los que pueden obtenerse por un desarrollo diligente de procesos, las preparaciones se repitieron si se necesitaba más material,

(vii) cuando se consignan, los datos NMR están en la forma de valores delta para los principales protones de diagnostico, dados en partes por millon (ppm) relativas a tetrametilsilano (TMS) como un estandar interno, determinado a 300 MHz usando sulfoxido de dimetilo de perdeuterio (DMSO-d_6) como disolvente, a menos que se indique lo contrario, ^{19}F NMR se registra igualmente en DMSO-d_6 a menos que se especifique otra cosa,

(viii) los simbolos quimicos tienen sus significados habituales, se emplean unidades y simbolos SI,

(ix) las relaciones de disolvente se dan en terminos de volumen volumen (v/v), y

(x) los espectros de masas se efectuaron con una energia electronica de 70 voltios electronicos en el modo de ionizacion quimica (CI) usando una sonda de exposicion directa, donde se indica, la ionizacion se efectuo mediante impacto de electrones (EI), bombardeo de atomos rapidos (FAB) o electrospray (electroatomizacion) (ESP), se dan los valores para m/z,

generalmente, solo se reportan los iones que indican la masa original, y a menos que se especifique lo contrario, el ion de masa citado es $(MH)^+$,

(xi) a menos que se especifique lo contrario, los compuestos que contienen un carbono asimétricamente sustituido y/o atomo de azufre no han sido resueltos,

(xii) donde describe una sintesis como análoga a la descrita en un ejemplo previo, las cantidades empleadas son las relaciones milimolares equivalentes a las usadas en el ejemplo previo,

(xvi) se han usado las siguientes abreviaturas

THF	tetrahidrofurano,
DMF	*N*,*N*-dimetilformamida,
DMFDMA	dimetilformamida dimetilacetal,
EtOAc	acetato de etilo,
MeOH	metanol,
EtOH	etanol,
DIPEA	*N*,*N*-diisopropiletilamina,
HATU	hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-1,1-3,3-tetrametiluronio,
HOBt	1-hidroxibenzotriazol
EDAC	eter dietilico de 1-etil-3-(3-dimetilaminopropil)carbodiimida clorhidrato,
TFA	ácido trifluoroacético,
DCM	diclorometano, y
DMSO	sulfóxido de dimetilo

xvii) donde se menciona una columna Isolute SCX-2, esto significa un cartucho de extraccion de "intercambio iónico" para adsorcion de compuestos basicos, es decir un tubo de polipropileno que contiene un sorbente fuerte de intercambio de cationes a base de acido bencenosulfonico, usado de acuerdo con las instrucciones de los

fabricantes, obtenido de International Sorbent Technologies Limited, Dyffryn Business Park, Hengeod, Mid Glamorgan, UK, CF82 7RJ,

xviii) donde se menciona una columna amina Isolute, esto significa un cartucho de extracción de "intercambio de iones" para la adsorcion de compuestos acidos, es decir, un tubo de polipropileno que contiene un aminosilano enlazado covalentemente a una particula de silice, usado de acuerdo con las instrucciones de los fabricantes, obtenido de International Sorbent Technologies Limited, Dyffryn Business Park, Hengeod, Mid Glamorgan, UK, CF82 7RJ,

xix) donde se menciona una columna Chemelut, esto significa un cartucho de extraccion para la remoción de agua, es decir, un tubo de polipropileno que contiene tierra de diatomeas, usado de acuerdo con las instrucciones de los fabricantes, obtenido de Varian, Harbor City, California, USA, y

xx) donde se realizó HPLC en una columna Phenomenex, esto se refiere a una columna Phenomenex 150 x 21 2 mm Luna 10 micrones C18 usando una gradiente de 5 a 95 de 0 2% TFA / agua / acetonitrilo durante 10 minutos con una velocidad de flujo de 20 ml/minuto,

xxi) resina de carbonato de poliestireno macroporoso se refiere a una resina de carbonato MP de Argonaut Technologies con la capacidad de 3 0 equivalentes molares por gramo de resina, obtenible de Argonaut Technologies, New Road, Hengoed, Mid Glamorgan Reino Unido, CF82 8AU

Ejemplo 1

2-[4-(4-Mesilpiperazin-1-il)anilin]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina

2-Amino-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina (Método 39 de WO 03/076436, 220mg, 1mmol), 1-bromo-4-(4-mesilpiperazinil)benceno (WO 2001062742, 319mg, 1mmol), tris(dibencilidenacetona)dipaladio (0) (23mg, 2mol%), 2-(di-*terc*-butilfosfino)bifenilo (6mg, 2 mol%) y *terc*-butoxido de sodio (135 mg, 1 4 mmol) en 1,4-dioxano anhidro (10ml) se vacio y se volvio a llenar con

nitrógeno (3 veces) La reaccion se calentó bajo nitrogeno a 95°C de un dia para otro antes de evaporar bajo presion reducida El residuo se trituro con EtOAc (20ml), se filtro y se re-evaporo para producir una goma Cromatografía en gel de silice con MeOH DCM (2 98 a 5 95) produjo el compuesto del titulo como un solido amarillo (70 mg 15%) NMR 1 39 (d, 6H), 2 47 (s, 3H), 2 92 (s, 3H), 3 17 (m, 4H), 3 26 (m, 4H), 5 70 (septuplete, 1H), 6 92 (d, 2H), 6 94 (d, 1H), 7 39 (s, 1H), 7 48 (d, 2H), 8 32 (d, 1H), 9 18 (s, 1H), m/z 456

Ejemplo 2

2-[4-(4-Mesilpiperazin-1-il)anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-cloropirimidina

El compuesto del titulo se preparo de acuerdo con el procedimiento de Ejemplo 1 usando 2-amino-5-cloro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina (Metodo 5) calentando durante 30 horas a 100°C Cromatografía en gel de silice con MeOH DCM (2 98 a 6 94) NMR 1 36 (d, 6H), 2 46 (s, 3H), 2 80 (s, 3H), 3 16 (m, 4H), 3 23 (m, 4H), 4 79 (septuplete, 1H), 6 91 (d, 2H), 7 22 (s, 1H), 7 49 (d, 2H), 8 51 (d, 1H), 9 49 (s, 1H), m/z 490

Ejemplo 3

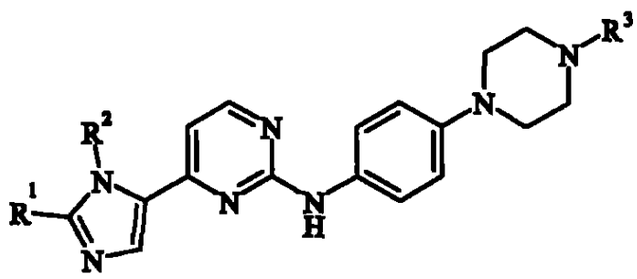
2-[4-(4-Mesilpiperazin-1-il)anilino]-4-(1-ciclobutil-2-metil-1*H*-imidazol-5-il)pirimidina

5-(3-Dimetilaminoprop-2-en-1-oil)-1-ciclobutil-2-metilimidazol (Metodo 37 de WO 03/076435, 233 mg 1 mmol) y N-{4-[4-(metilsulfonil)piperazin-1-il]fenil}guanidina (Metodo 1, 390 mg 1 3mmol) en 2-metoxietanol (8 ml) se agito y se calento por 18 horas a 110°C La mezcla de reacción se evaporo bajo presion reducida y el residuo se purifico por cromatografía en gel de silice con MeOH DCM (3 97 a 8 92) Luego de la evaporación y trituración con eter, el compuesto del titulo se obtuvo como un solido amarillo (227 mg 48 5%) NMR 1 60-1 71 (2xm, 2H), 2 36 (m, 4H), 2 49 (s, 3H), 2 91 (s, 3H), 3 18 (m, 4H), 3 25 (m, 4H), 5 51

(quintete, 1H), 6 91 (d, 1H), 6 97 (d, 2H), 7 30 (s, 1H), 7 54 (d, 2H), 8 33 (d, 1H), 9 23 (s, 1H), m/z 468

Ejemplos 4-17

Los siguientes compuestos se prepararon por el procedimiento de Ejemplo 3 usando el imidazol apropiado y *N*-{4-[4-(metilsulfonil)piperazin-1-il]fenil}guanidina (Método 1) o sal bicarbonato de *N*-[4-(4-acetilpiperazin-1-il)fenil]guanidina (Metodo 2)



Ej	R^1	R^2	R^3	NMR	m/z	SM
4[1]	Me	Ciclopropil-metilo	$MeSO_2$	0 09 (m, 2H), 0 28 (m, 2H), 1 00 (m, 1H), 2 39 (s, 3H), 2 92 (s, 3H), 3 18 (m, 4H) 3 24 (m, 4H), 4 49 (d, 2H), 6 94 (d, 2H) 7 02 (d, 1H), 7 47 (d, 2H), 7 58 (s, 1H), 8 30 (d, 1H) 9 15 (s, 1H)	468	Mét 41 in WO 03/076435
5[2]	Et	Et	$MeSO_2$-	1 11 (t, 3H), 1 24 (t, 3H), 2 71 (q, 2H), 2 91 (s, 3H), 3 18 (m, 4H), 3 23 (m, 4H), 4 50 (q, 2H), 6 95 (d, 2H), 7 03 (d, 1H), 7 47 (d, 2H), 7 61 (s, 1H), 8 28 (d, 1H), 9 12 (s, 1H)	456	Mét. 55 de WO 03/076434

Ej	R^1	R^2	R^3	NMR	m/z	SM
6[3]	Et	*i*-Pr	$MeSO_2$-	1 28 (t, 3H), 1 40 (d, 6H), 2 79 (q, 2H) 2 91 (s, 3H), 3 17 (m, 4H), 3 24 (m, 4H) 5 61 (septuplete, 1H), 6 93 (d, 2H), 6 94 (d, 1H), 7 40 (s, 1H), 7 49 (d, 2H), 8 32 (d, 1H) 9 18 (s, 1H)	470	Met. 9
7[4]	$MeOCH_2$-	*i*-Pr	$MeSO_2$-	1 42 (d, 6H), 2 92 (s, 3H), 3 17 (m, 4H) 3 24 (m 4H), 3 27 (s 3H) 4 53 (s, 2H), 5 52 (septuplete, 1H), 6 94 (d 2H), 6 99 (d, 1H), 7 47 (s, 1H), 7 49 (d, 2H), 8 38 (d, 1H), 9.21 (s, 1H)	486	Mét. 50 de WO 03/076434
8[5]	Pr	Et	$MeSO_2$-	0 97 (t, 3H), 1 12 (t,3H), 1 72 (sextuplet, 2H), 2 68 (t, 2H), 2 92 (s, 3H), 3 16 (m, 4H), 3 27 (m, 4H) 4 51 (q, 2H), 6 93 (d, 2H), 7 02 (d, 1H), 7 48 (d, 2H), 7 62 (s, 1H), 8 29 (d, 1H), 9 12 (s, 1H)	470	Mét. 13
9[6]	Me	Et	$MeSO_2$-	1 12 (t, 3H), 2 38 (s,3H), 2 91 (s, 3H), 3 17 (m 4H), 3 24 (m 4H) 4 50 (q, 2H), 6 94 (d, 2H) 7 02 (d, 1H), 7 48 (d, 2H), 7 60 (s, 1H), 8 29 (d, 1H), 9 13 (s, 1H)	442	Mét. 16 de WO 02/20512

Ej	R^1	R^2	R^3	NMR	m/z	SM
107	Me	*t*-Bu	$MeSO_2$-	0 60 (d, 6H), 1 69 (septuplete, 1H) 2 36 (s, 3H), 2 92 (s, 3H), 3 16 (m, 4H), 3 25 (m, 4H), 4 32 (d, 2H), 6 94 (d, 2H), 7 01 (d, 1H) 7 47 (d, 2H), 7 58 (s, 1H), 8 29 (d, 1H), 9 18 (s, 1H)	470	Mét. 29 de WO 03/07643
118	Et	*t*-Pr	MeC(O)-	1 28 (t, 3H), 1 40 (d, 6H), 2 02 (s, 3H), 2 79 (q, 2H) 3 00 (t, 2H), 3 08 (t, 2H), 3 57 (m, 4H), 5 60 (septuplete, 1H), 6 91 (d, 2H), 6 94 (d, 1H) 7 41 (s, 1H) 7 48 (d, 2H), 8 31 (d, 1H), 9 18 (s, 1H)	434	Met 9
12	Pr	Et	MeC(O)-	0 95 (t,3H), 1 10 (t,3H), 1 70 (septuplete, 2H), 2 02 (s, 3H), 2 68 (t, 2H), 3 01 (t, 2H), 3 08 (t,2H), 3 59 (q, 4H), 4 51 (q,2H) 6 92 (d, 2H), 7 02 (d 1H) 7 44 (d, 2H), 7 62 (s, 1H), 8 29 (d, 1H) 9 11(s 1H)	434	Mét. 13
13	Me	Ciclobutilo	MeC(O)-	1 60 (sextet, 1H), 1 73 (q, 1H), 2 05 (s, 3H), 2 30-2 48 (m, 4H), 3 031 (t, 2H), 3 09 (t, 2H), 3 59 (q, 4H) 5 58	432	Met. 37 de WO 03/07643 5

Ej	R^1	R^2	R^3	NMR	m/z	SM
				(quintete, 1H), 6 93 (d, 1H), 6 96 (d, 2H), 7 32 (s, 1H), 7 57 (d, 2H) 8 34 (d, 1H), 9 24 (s, 1H)		
14	Et	Et	MeC(O)-	1 12 (t, 3H), 1 24 (t, 3H), 2 03 (s, 3H), 2 71 (q, 2H), 3 01 (t, 2H) 3 08 (t, 2H), 3 57 (q, 4H), 4 49 (q 2H), 6 92 (d, 2H), 7 01 (d, 1H), 7 45 (d, 2H) 7 61 (s, 1H), 8 29 (d, 1H), 9 10 (s, 1H)	420	Met. 55 de WO 03/076434
15	Me	Et	MeC(O)-	1 11 (t, 3H), 2 03 (s 3H), 2 38 (s, 3H), 3 02 (t, 2H), 3 08 (t, 2H), 3 57 (q, 4H), 4 50 (q, 2H), 6 92 (d, 2H), 7 01 (d, 1H), 7 46 (d, 2H) 7 59 (s, 1H), 8 28 (d, 1H), 9 09 (s, 1H)	406	Mét 16 de WO 02/20512
169	$MeOCH_2$-	*i*-Pr	MeC(O)-	1 42 (d,6H), 2 03 (s 3H), 3 01 (t, 2H), 3 08 (t, 2H), 3 27 (s, 3H), 3 57 (q, 4H), 4 53 (s 2H), 5 52 (septuplete, 1H), 6 91 (d, 2H), 6 99 (d, 1H), 7 44 (s, 1H), 7 47 (d, 2H), 8 38 (d, 1H), 9 20 (s, 1H)	450	Met 50 de WO 03/076434
17	Me	*i*-Bu	MeC(O)-	0 60 (d, 6H), 1 69	434	Mét. 29

Ejemplo 18

2-[4-(4-Acetilpiperazin-1-anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina

(2*E*)-3-(Dimetilamino)-1-(1-isopropil-2-metil-1*H*-imidazol-5-il) prop-2-en-1-ona (Metodo 24 de WO 03/076436, 140 mg 0 63 mmol) y sal bicarbonato de N-[4-(4-acetilpiperazin-1-il)fenil]guanidina (Metodo 2, 240 mg 0 74 mmol) en 2-metoxietanol (4 ml) se hicieron reaccionar bajo nitrogeno bajo condiciones de microondas a 200°C por 30 minutos Luego de la evaporación bajo presión reducida, cromatografía en gel de silice con MeOH DCM (2 98 a 6 94) produjo el compuesto del titulo, luego de trituración con éter, como un solido amarillo (85 mg 31 5%) NMR 1 39 (d, 6H), 2 02 (s, 3H), 2 45 (s, 3H), 3 00 (b t, 2H), 3 06 (b t, 2H), 3 56 (b q, 4H), 5 70 (septuplete, 1H), 6 91 (d, 2H), 6 95 (d, 1H), 7 38 (s, 1H), 7 46 (d, 2H), 8 31 (d, 1H), 9 15 (s, 1H), m/z 420

Ejemplo 19

2-[4-(4-Acetilpiperazin-1-il)anilin]-4-[1-(ciclopropilmetil)-2-metil-1*H*-imidazol-5-il]pirimidina

El compuesto del titulo se preparo mediante el procedimiento de Ejemplo 18 de 5-(3-dimetilaminoprop-2-en-1-oil)-1-ciclopropilmetil-2-metilimidazol (Metodo 41 en WO 03/076435) excepto que la reacción se calento en microondas a 200°C por 40 minutos 148 mg 53 4% NMR 0 10 (m, 2H), 0 28 (m, 2H), 1 02 (m, 1H), 2 03 (s, 3H), 2 38 (s, 3H), 3 01 (t, 2H), 3 08 (t, 2H), 3 57 (q, 4H), 4 48 (d, 2H), 6 92 (d, 2H), 7 01 (d, 1H), 7 43 (d, 2H), 7 57 (s, 1H), 8 281 (d, 1H), 9 12 (s, 1H), m/z 432

Ejemplo 20

2-[4-(Piperazin-1-il)anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-pirimidina

2-[4-(4-Acetilpiperazin-1-il)amino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina (Ejemplo 18, 1 3g) se agito y se calento en isopropanol (15ml) y 33% de ácido clorhídrico (1 5ml) a 90°C por 4 5

horas La reacción se evaporo bajo presión reducida y luego se basifico con 7N de amoniaco en MeOH y se re-evaporo Se agrego tolueno y la mezcla se re-evaporo (3 veces) El residuo se purificó por cromatografía en oxido de aluminio neutro, actividad II eluyendo con MeOH DCM (5 95) para producir el compuesto del titulo como una goma amarilla (330 mg 28%) NMR 1 40 (d, 6H), 2 46 (s, 3H), 2 82 (m, 4H), 2 96 (m, 4H), 5 69 (septuplete, 1H), 6 85 (d, 2H), 6 93 (d, 1H), 7 18 (s, 1H), 7 42 (d, 2H), 8 30 (d, 1H), 9 11 (s, 1H), m/z 378

Ejemplo 21

2-{4-[4-(2-Acetoxiacetil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5il)pirimidina

2-[4-(Piperazin-1-il)anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina (Ejemplo 20, 330mg 0 88 mmol) se agitó en DCM (6ml) a temperatura de la sala Se agregó trietilamina (153mg 1 51 mmol) seguida por la adicion gota a gota de cloruro de acetoxiacetilo (143 mg 1 05 mmol) Luego de agitar por 1 25 horas, se agregaron DCM (10 ml) y salmuera (5 ml) La reaccion se agito vigorosamente por 10 minutos, luego las capas organicas se separaron, se secaron y se evaporaron bajo presión reducida para producir el compuesto del titulo como una espuma amarilla Rendimiento cuantitativo El solido se trituro con eter y se re-evaporo NMR 1 40 (d, 6H), 2 08 (s, 3H), 2 48 (s, 3H), 3 05 (b d, 4H), 3 54 (b d, 4H), 4 81 (s, 2H), 5 70 (septuplete, 1H), 6 92 (d, 2H), 6 95 (d, 1H), 7 40 (s, 1H), 7 48 (d, 2H), 8 31 (d, 1H), 9 18 (s, 1H), m/z 478

Ejemplo 22

2-{4-[4-(2-Hidroxiacetil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina

2-{4-[4-(2-Acetoxiacetil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina (Ejemplo 21, 330mg) se agito en MeOH (5 ml) a temperatura de la sala y se agrego 7N de amoniaco en MeOH (1 6 ml) Luego de 28 horas, la reaccion se evaporo bajo presion reducida

Cromatografía en gel de sílice usando MeOH DCM (4 96 a 5 95), produjo el compuesto del título como un sólido amarillo (108 mg 36%) NMR 1 39 (d, 6H), 2 46 (s, 3H), 3 05 (b s, 4H), 3 48 (b s, 2H), 3 61 (b s, 2H), 4 12 (d, 2H), 4 57 (t, 1H), 5 69 (septuplete, 1H), 6 92 (d, 2H), 6 95 (d, 1H), 7 38 (s, 1H), 7 47 (d, 2H), 8 31 (d, 1H), 9 15 (s, 1H), m/z 436

Ejemplo 23

2-{4-[4-(2-Dimetilaminoacetil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina

Cloruro de cloroacetilo (50 µl, 0 65 mmol) se agregó gota a gota a una solución agitada de 2-[4-(piperazin-1-il)anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina (Ejemplo 20, 200 mg, 0 53 mmol) y trietilamina (90 µl, 0 65 mmol) en DCM (5 ml) a temperatura de la sala Luego de 50 minutos, se agrego 2M de dimetilamina en solucion de THF (2 ml, 4mmol) y la reaccion se agito por 5 horas antes de evaporar bajo presion reducida. Cromatografía en óxido de aluminio neutro (actividad II) con MeOH DCM (1 99 a 3 97) produjo un material que requirio purificacion posterior en gel de sílice con MeOH DCM 7N NH_3 MeOH (3 97 0025 a 10 90 0025) para producir el compuesto del título como una espuma amarilla (150 mg 60% de rendimiento) NMR 1 39 (d, 6H), 2 19 (s, 6H), 2 46 (s, 3H), 3 02 (b t, 2H), 3 06 (b t, 2H), 3 59 (b t, 2H), 3 68 (b t, 2H), 5 69 (septuplete, 1H), 6 92 (d, 2H), 6 94 (d, 1H), 7 39 (s, 1H), 7 47 (d, 2H), 8 31 (d, 1H), 9 17 (s, 1H), m/z 463

Ejemplo 24

2-{4-[4-(Cloroacetil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina

2-[4-(Piperazin-1-il)anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina (Ejemplo 20,1 89g, 5 mmol), di-isopropiletilamina (0 956 ml, 5 5 mmol) en DCM (25 ml) se trató a 0°C con cloruro de cloroacetilo (0 438 ml, 5 5 mmol) La mezcla se agitó a temperatura ambiente por 2 horas, se diluyó con DCM (25 ml), se lavo con solución de bicarbonato de sodio

saturado acuoso (20 ml) y solución de cloruro de sodio saturado acuoso (20 ml) La solución se secó y se evaporó bajo presion reducida para producir el compuesto del titulo, (1 96g, 87%) NMR ($CDCl_3$) 8 30 (d, 1H), 7 44 (d, 2H), 7 35 (s, 1H), 6 96 (s, 1H), 6 92 (d, 1H), 6 85 (d, 1H), 5 68-5 56 (m, 1H), 4 12 (s, 2H), 3 83-3 76 (m, 2H), 3 72-3 67 (m, 2H), 3 22- 3 11 (m, 4H), 2 59 (s, 3H), 1 48 (d, 6H), m/z 454

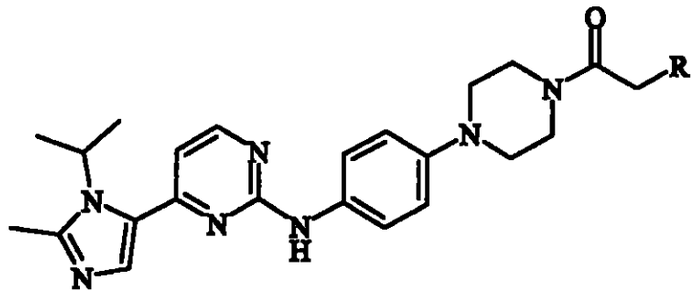
Ejemplo 25

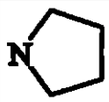
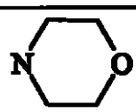
2-{4-[4-(Azetidin-1-ilacetil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina clorhidrato

2-{4-[4-(Cloroacetil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol- 5-il)pirimidina (Ejemplo 24, 0 34g, 0 75mmol) y azetidina (2ml) se agito por 24 horas a temperatura ambiente La solucion se diluyó con EtOAc (20ml), se lavó con solución de bicarbonato de sodio saturado acuoso (10 ml) y solución de cloruro de sodio saturado acuoso (10 ml), luego se seco y se evaporo a presion reducida El residuo se purifico por cromatografía en una columna de silice de 40g, se eluyo con una gradiente 3% MeOH-amoniaco/DCM a 5% MeOH-amoniaco/DCM, para producir la amina, la cual se convirtio en la sal clorhidrato disolviendo en EtOAc (3 ml) y tratando con 1 0 solución molar de HCl etereo (0 75 ml) El solido se trituro con eter (20 ml) y se filtro para producir el compuesto del titulo (24mg, 7%) NMR 9 77 (s, 1H), 8 58 (d, 1H), 8 20 (s, 1H), 7 61 (d, 2H), 7 35- 7 24 (m, 2H), 7 13 (d, 1H), 5 64-5 55 (m, 1H), 4 65 (brs, 1H), 4 44 (d, 2H), 4 23-4 11 (m, 2H), 4 09-3 96 (m, 2H), 3 81-3 71 (m, 2H), 3 69-3 59 (m, 2H), 3 42-3 31 (m, 2H), 3 30-3 17 (m, 2H), 2 48-2 24 (m, 2H), 2 81 (s, 3H), 1 48 (d, 6H), m/z 475

Ejemplos 26-28

Las siguientes sales se prepararon usando el procedimiento de Ejemplo 25 de 2-{4-[4-(cloroacetil)piperazin-1-il]amino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina Ejemplo 24) y la amina apropiada.



Ej	R	NMR	m/z	Sal
26		10 29 (brs, 1H), 9 91 (s, 1H), 8 60 (d, 1H), 8 23 (s, 1H), 7 68 (d, 2H), 7 53 - 7 42 (m, 2H), 7 17 (d, 1H), 5 65 -5 56 (m, 1H), 4 48 (d, 2H), 3 94 (s, 2H), 3 80 (s, 2H), 3 64 - 3 53 (m, 2H), 3 51 (s, 2H), 3 41 - 3 31 (m, 2H), 3 18 - 3 02 (m, 2H), 2 83 (s, 3H), 2 06 -1 84 (m, 4H), 1 49 (d, 6H)	489	HCl
27		9 90 (s, 1H), 8 60 (d, 1H), 8 22 (s, 1H), 7 66 (d, 2H), 7 48 - 7 37 (m, 2H), 7 16 (d, 1H), 5 65 - 5 55 (m, 1H), 4 99 (s, 2H), 4 53 (s, 1H), 4 01 - 3 70 (m, 8H), 3 51 -3 41 (m, 4H), 3 38 - 3 31 (m, 2H), 3 27 - 3 12 (m, 2H), 2 82 (s,3H), 1 49 (d, 6H)	505	HCl
28	$N(Et)_2$	9 98 (s, 1H), 9 57 (s, 1H), 8 61 (d, 1H), 8 23 (s, 1H), 7 71 (d, 2H), 7 52 (d, 2H), 7 18 (d, 1H), 5 65 - 5 56 (m, 1H), 4 38 (d, 2H), 3 98 - 3 78 (m, 4H), 3 55 - 3 37 (m, 4H), 3 24 - 3 12 (m, 4H), 2 83 (s, 3H), 1 50 (d, 6H), 1 24 (t, 6H)	491	HCl

Ejemplo 29

2-{4-[4-(vinilsulfonil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina

2-[4-(Piperazin-1-il)anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina (Ejemplo 20, 370mg 0 98 mmol) se agitó en DCM (10 ml) a temperatura de la sala Se agrego trietilamina (150mg 1 49 mmol) seguida

por la adicion gota a gota de cloruro de 2-cloro-1-etansulfonilo (196 mg 1 2 mmol) en DCM (1 ml) Luego de agitar por 1 25 horas, la reaccion se evaporo bajo presion reducida y se trituró con eter El sólido resultante se trato con agua (15 ml), se basifico con solucion de bicarbonato de sodio saturado y se extrajo en DCM (2x20 ml) Los organicos se lavaron con salmuera (10 ml), se secaron y se evaporaron para producir una goma Luego de la cromatografía en gel de silice usando MeOH DCM (3 97 a 5 95), el compuesto del titulo se obtuvo como un solido amarillo (140 mg 30 4%) NMR 1 39 (d, 6H), 2 46 (s, 3H), 3 16 (s, 8H), 5 68 (septuplete, 1H), 6 20 (d, 1H), 6 85 (dd, 1H), 6 91 (d, 2H), 6 95 (d, 1H), 7 38 (s, 1H), 7 47 (d, 2H), 8 30 (d, 1H), 9 16 (s, 1H), m/z 468

Ejemplo 30

2-{4-[4-(2-Dimetilaminoetilsulfonil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina

Dimetilamina (2 0M) en THF (1 5 ml) se agrego a una suspension agitada de 2-{4-[4-(vinilsulfonil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina (Ejemplo 29, 140 mg 0 3 mmol) en THF (3 ml) a temperatura de la sala Se agregó más solución de dimetilamina (0 5 ml) luego de 2 horas La reacción se agito durante 1 hora, luego se dejo reposar de un dia para otro La reaccion se evaporo bajo presion reducida, se trituró con éter y se filtro para producir el compuesto del titulo como un solido amarillo (134mg 89%) NMR 1 40 (d, 6H), 2 46 (s, 3H), 2 62 (t, 2H), 3 13 (t, 4H), 3 20-3 35 (2H y 4H) [bajo intercambiables], 5 68 (septuplete, 1H), 6 92 (d, 2H), 6 95 (d, 1H), 7 38 (s, 1H), 7 47 (d, 2H), 8 31 (d, 1H), 9 18 (s, 1H) [+ácido deuteroacético 3 01 (b d, 2H), 3 14 (t, 4H), 3 33 (t, 4H), 3 37 (m, 2H)], m/z 478

Ejemplo 31

2-{4-[4-(2-Metoxietilsulfonil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina

Metoxido de sodio (40 mg 0 74 mmol) se agrego a 2-{4-[4-(vinilsulfonil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina (Ejemplo 29, 300 mg 0 64 mmol) en MeOH (4 ml) Luego de agitar a temperatura de la sala por 5 horas, la reaccion se evaporo Luego de la cromatografía en gel de silice usando MeOH DCM EtOAc (5 47 5 47 5) y trituracion con eter, el compuesto del titulo se obtuvo como un solido amarillo

NMR 1 41 (d, 6H), 2 47 (s, 3H), 3 13 (m, 4H), 3 26 (4H junto con intercambiables), 3 37 (t, 2H), 3 67 (t, 2H), 5 69 (septuplete, 1H), 6 93 (d, 2H), 6 96 (d, 1H), 7 39 (s, 1H), 7 49 (d, 2H), 8 32 (d, 1H), 9 18 (s, 1H), m/z 500

Ejemplo 32

2-{4-(2-Hidroxietilsulfonil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina

Una mezcla de 2-{4-[4-(vinilsulfonil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina (Ejemplo 29, 260 mg 0 56 mmol) e hidróxido de bario (560 mg 3 27 mmol) en agua (10 ml) se calento a 65°C - 90°C durante 6 horas Se agregó 1,4-dioxano (1 ml) despues de 1,2, 3 y 5 horas Luego de la evaporacion bajo presion reducida, el residuo se trató con agua (10 ml) y solución de bicarbonato de sodio saturado (10 ml) La suspensión se extrajo con DCM (30 ml y 2x20 ml) y EtOAc (25 ml) Los dos extractos se lavaron (separadamente) con salmuera (10 ml) y se secaron (Na_2SO_4) Los extractos se combinaron y se evaporaron Luego de la cromatografía en gel de silice usando MeOH DCM (4 96 a 8 92), el compuesto del titulo se obtuvo como un solido amarillo (108 mg 40%)

NMR 1 40 (d, 6H), 2 49 (s, 3H), 3 13 (m, 4H), 3 23 (t, 2H), 3 30 (m, 4H), 3 76 (q, 2H), 5 01 (t, 1H), 5 69 (septuplete, 1H), 6 93 (d, 2H), 6 96 (d, 1H), 7 39 (s, 1H), 7 48 (d, 2H), 8 31 (d, 1H), 9 18 (s, 1H), m/z 486

Ejemplo 33

2-[4-(4-Acetilpiperazin-1-il)anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-cloropirimidina

(2*E*)-2-Cloro-3-(dimetilamino)-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona (1 68g de Metodo 3 - 5mmol asumidos) y sal bicarbonato de *N*-[4-(4-acetilpiperazin-1-il)fenil]guanidina (Metodo 2) (1 94g 6mmol) en 2-metoxietanol (25ml) se calentaron bajo nitrogeno a 110°C por 3 5 horas antes de la evaporacion bajo presion reducida El residuo se purificó por cromatografía en gel de silice con MeOH DCM (3 97 a 5 95) para producir el compuesto del titulo, luego de trituración con éter, como una de espuma. NMR 1 36 (d, 6H), 2 02 (s, 3H), 2 48 (s, 3H), 3 00 (b t, 2H), 3 08 (b t, 2H), 3 56 (b q, 4H), 4 80 (septuplete, 1H), 6 90 (d, 2H), 7 21 (s, 1H), 7 47 (d, 2H), 8 50 (s, 1H), 9 48 (s, 1H), m/z 454

Ejemplo 34

2-[4-(Piperazin-1-il)anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-cloropirimidina

El compuesto del titulo se preparo de 2-[4-(4-acetilpiperazin-1-il) anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-cloropirimidina (Ejemplo 33, 800mg) por el metodo de Ejemplo 20, excepto que tras la purificación por cromatografía en oxido de aluminio neutro, actividad II eluyendo con MeOH DCM (3 97), se aisló el compuesto del título como una goma amarilla La trituracion con éter produjo una espuma (50mg 7%) NMR 1 34 (d, 6H), 2 45 (s, 3H), 2 82 (m, 4H), 2 96 (m, 4H), 4 82 (septuplete, 1H), 6 85 (d, 2H), 7 41 (s, 1H), 7 42 (d, 2H), 8 49 (s, 1H), 9 43 (s, 1H), m/z 412

Ejemplo 35

2-{4-[4-(Acetoxiacetil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il-5-cloropirimidina

El compuesto del título se preparó usando el procedimiento de Ejemplo 21 empleando 400mg 0 97 mmol de 2-[4-(piperazin-1-il)anilino]-

4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-cloropirimidina (Ejemplo 34) Luego del desarrollo, la mezcla se purifico por cromatografía en gel de silice usando MeOH DCM (3 97 a 6 94) para producir un solido (230 mg) NMR 1 35 (d, 6H), 2 08 (s, 3H), 2 48 (s, 3H), 3 04 (b d, 4H), 3 52 (b d, 4H), 4 80 (septuplete, 1H), 4 81 (s, 2H), 6 92 (d, 2H), 7 22 (s, 1H), 7 48 (d, 2H), 8 51 (d, 1H), 9 49 (s, 1H), m/z 512

Ejemplo 36

2-{4-[4-(Hidroxiacetil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-cloropirimidina

2-{4-[4-(Acetoxiacetil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-cloropirimidina (Ejemplo 35) se desprotegio por el procedimiento de Ejemplo 22 La mezcla de reaccion se evaporó bajo presión reducida El residuo se disolvio en DCM (30 ml), se lavo con agua (15ml) y salmuera (15ml), se secó y se evaporo El residuo se trituro con eter y se re-evaporo para producir el compuesto del titulo como un solido (180 mg) NMR 1 34 (d, 6H), 2 48 (s, 3H), 3 03 (b s, 4H), 3 52 (b d, 4H), 4 11 (d, 2H), 4 59 (t, 1H), 4 80 (septuplete, 1H), 6 91 (d, 2H), 7 21 (s, 1H), 7 47 (d, 2H), 8 51 (s, 1H), 9 49 (s, 1H), m/z 470

Ejemplo 37

2-{4-[4-(2-Hidroxi-2-metilpropionil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-cloropirimidina

Acido 2-hidroxiisobutirico (162 mg 1 mmol) se agregó a una solucion de 1,1'-carbonildiimidazol (162 mg 1 mmol) en DCM (4 ml) y se agito a temperatura de la sala por 15 minutos Una solucion de 2-[4-(piperazin-1-il)anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-cloropirimidina (Ejemplo 34 400 mg 0 97 mmol) en DCM (8 ml) se agrego y la agitacion se continuó por 19 horas Se agrego DCM (8 ml) y la capa organica se lavó con 5% (v/v) de ácido acetico (15 ml), agua (15 ml), salmuera (15 ml) y se seco antes de evaporar bajo presión reducida Cromatografía en gel de silice con MeOH DCM (4 96 a 8 92) produjo el

compuesto del título, luego de la trituracion con éter, como un solido (67 mg 14%) NMR (500MHz) 1 30 (d, 6H), 1 34 (d, 6H), 2 48 (s, 3H), 3 04 (t, 4H), 3 62 (b s, 4H), 4 00 (b s, 4H), 4 79 (septuplete, 1H), 5 41 (s, 1H), 6 90 (d, 2H), 7 22 (s, 1H), 7 48 (d, 2H), 8 51 (s, 1H), 9 49 (s, 1H), m/z 498

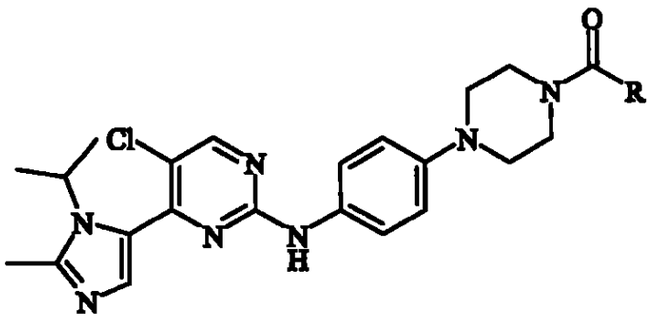
Ejemplo 38

2-{4-[4-(2-(S)-2-Hidroxipropionil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-cloropirimidina

A una solución de 2-[4-(piperazin-1-il)anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-cloropirimidina (Ejemplo 34, 276mg, 1 00mmol) en DMF (7ml) se agregó ácido L-lactico (90mg, 1 50mmol), y DIPEA (245 µl, 181mg, 2 1mmol) Una solución de HATU (330mg, 1 30mmol) en DMF (3ml) se agrego gota a gota, luego la mezcla se agito a temperatura ambiente por 20 horas La solucion se concentró *in vacuo*, a continuación el residuo se disolvio en EtOAc (20ml), y se lavó con solucion de bicarbonato de sodio acuoso (15ml), luego salmuera (15ml) El extracto orgánico se secó y se concentró El residuo se purificó por cromatografía en gel de silice con 2N NH_3-MeOH DCM (3 97 a 5 95) para producir el compuesto del titulo como un solido blanco (233mg, 72%) NMR 1 37 (d, 3H), 1 45 (d, 6H), 2 58 (s, 3H), 3 12-3 17 (m, 4H), 3 56-3 60 (m, 2H), 3 75-3 92 (m, 3H), 4 48-4 54 (m, 1H), 4 96 (quintete, 1H), 6 91 (d, 2H), 6 94 (s, 1H), 7 43 (d, 2H), 7 50 (s, 1H), 8 38 (s, 1H), m/z 484

Ejemplos 39-47

Los siguientes compuestos se prepararon por el procedimiento de Ejemplo 38 usando el acido apropiado y 2-[4-(piperazin-1-il)anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-cloropirimidina (Ejemplo 34)

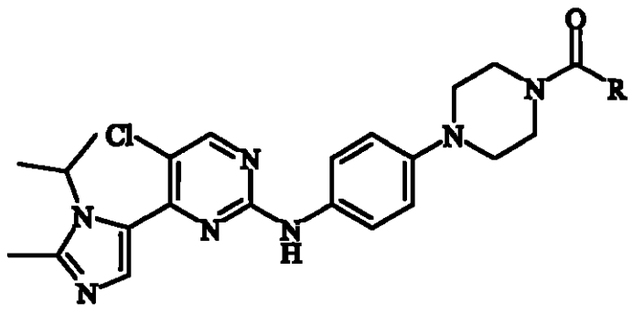


Ej	R	NMR (300MHz, $CDCl_3$)	m/z
39	(*R*)-MeCH(OH)-	1 37 (d, 3H), 1 45 (d, 6H), 2 58 (s, 3H), 3 12-3 17 (m, 4H), 3 56-3 60 (m, 2H), 3 75-3 92 (m, 3H), 4 48-4 54 (m, 1H), 4 96 (quintete, 1H), 6 91 (d, 2H), 6 94 (s, 1H), 7 43 (d, 2H), 7 50 (s, 1H), 8 38 (s,	484
40	$MeOCH_2$-	1 43 (d, 6H), 2 57 (s, 3H), 3 10-3 15 (m, 4H), 3 44 (s, 3H), 3 65-3 69 (m, 2H), 3 76-3 80 (m, 2H), 4 15 (s, 2H), 4 93 (quintete, 1H), 6 91 (d, 2H), 6 94 (s, 1H), 7 41 (d, 2H), 7 50 (s, 1H), 8 37 (s, 1H)	484
41	1-Hidroxiciclopropil-	(d6-DMSO) 0 74-0 78 (m, 2H), 0 90-0 95 (m, 2H), 1 34 (d, 6H), 2 46 (s, 3H), 3 04-3 08 (m, 4H), 3 68-3 80 (m, 4H), 4 79 (quintete, 1H), 6 33 (s, 1H), 6 91 (d, 2H), 7 21 (s, 1H), 7 45, (d, 2H), 8 50 (s, 1H), 9 48 (s, 1H)	496
42	(*R*)-MeCH(OMe)-	1 42-1 46 (m, 9H), 2 58 (s, 3H), 3 11-3 16 (m, 4H), 3 37 (s, 3H), 3 78-3 86 (m, 4H), 4 20 (q, 1H), 4 94 (quintete, 1H), 6 91 (d, 2H), 6 93 (s, 1H), 7 42 (d, 2H), 7 51 (s, 1H), 8 38 (s, 1H)	498

Ej	R	NMR (300MHz, $CDCl_3$)	m/z
43	(*S*)-MeCH(OMe)-	1 42-1 46 (m, 9H), 2 58 (s, 3H), 3 11-3 16 (m, 4H), 3 37 (s, 3H), 3 78-3 86 (m, 4H), 4 20 (q, 1H), 4 94 (quintete, 1H), 6 91 (d, 2H), 6 93 (s, 1H), 7 42 (d, 2H), 7 51 (s, 1H), 8 38 (s, 1H)	498
44	(*S*)-$MeCH_2CH(OH)$-	1 01 (t, 3H), 1 43 (d, 6H), 1 49-1 58 (m, 1H), 1 69-1 78 (m, 1H), 2 57 (s, 3H), 3 11-3 15 (m, 4H), 3 55-3 59 (m, 2H), 3 70-3 90 (m, 3H), 4 34-4 38 (m, 1H), 4 92 (quintete, 1H), 6 91 (d, 2H), 6 96 (s, 1H), 7 42 (d, 2H), 7 51 (s, 1H), 8 37 (s, 1H)	498
45	MeCH(Me)-	1 17 (d, 6H), 1 44 (d, 6H), 2 58 (s, 3H), 2 82-2 89 (m, 1H), 3 09-3 15 (m, 4H), 3 66-3 72 (m, 2H), 3 76-3 82 (m, 2H), 4 94 (quintete, 1H), 6 91 (d, 2H), 6 93 (s, 1H), 7 41 (d, 2H), 7 51 (s, 1H), 8 38 (s, 1H)	482
46	Ciclopropil-	0 77-0 83 (m, 2H), 1 00-1 05 (m, 2H), 1 44 (d, 6H), 1 74-1 81 (m, 1H), 2 58 (s, 3H), 3 11-3 19 (m, 4H), 3 79-3 87 (m, 4H), 4 94 (quintete, 1H), 6 91 (d, 2H), 6 94 (s, 1H), 7 41 (d, 2H), 7 51 (s, 1H), 8 37 (s, 1H)	480
47	(*R*)-$MeCH_2CH(OH)$-	1 01 (t, 3H), 1 43 (d, 6H), 1 49-1 58 (m, 1H), 1 69-1 78 (m, 1H), 2 57 (s, 3H), 3 11-3 15 (m, 4H), 3 55-3 59 (m, 2H), 3 70-3 90 (m, 3H), 4 34-4 38 (m, 1H), 4 92 (quintete, 1H), 6 91 (d, 2H), 6 96 (s, 1H), 7 42 (d, 2H), 7 51 (s, 1H), 8 37 (s, 1H)	498

Ejemplos 48-64

Los siguientes compuestos se prepararon por el procedimiento de Ejemplo 38 usando el acido apropiado y 2-[4-(piperazin-1-il)anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-cloropirimidina (Ejemplo 34) Las bases aisladas libres se disolvieron entonces en EtOAc (3ml) con la adicion de unas cuantas gotas de MeOH para contribuir a la disolucion Se agrego 1 0M de cloruro de hidrogeno en solucion de eter (1 equivalente), y las sales clorhidrato resultantes se trituraron con eter, luego se filtraron y se secaron *in vacuo*



Ej	R	NMR	m/z
48	$MeOCH_2CH_2$-	1 42 (d, 6H), 2 48 (s, 3H), 2 63 (t, 2H), 2 79 (s, 3H), 3 23-3 30 (m, 4H), 3 57 (t, 2H), 3 77-3 82 (m, 4H), 4 80 (quintete, 1H), 7 34-7 38 (m, 2H), 7 62 (d, 2H), 7 99 (s, 1H), 8 76 (s, 1H), 10 08 (brs, 1H)	498
49	1-Cianocicloprop-1-il-	1 42 (d, 6H), 1 52-1 56 (m, 2H), 1 60-1 64 (m, 2H), 2 78 (s, 3H), 3 27-3 33 (m, 4H), 3 85-3 91 (m, 4H), 4 80 (quintete, 1H), 7 24 (d, 2H), 7 59 (d, 2H), 7 98 (s, 1H), 8 74 (s, 1H), 10 01 (brs, 1H)	505
50	(*R*)-Tetrahidrofur-2-il-	1 42 (d, 6H), 1 79-1 87 (m, 2H), 1 98-2 11 (m, 2H), 2 78 (s, 3H), 3 19-3 27	510

Ej	R	NMR	m/z
		(m, 4H), 3 70-3 83 (m, 6H), 4 70 (dd, 1H), 4 80 (quintete, 1H), 7 23-7 30 (m, 2H), 7 59 (d, 2H), 7 98 (s, 1H), 8 74 (s, 1H), 10 02 (brs, 1H)	
51	(*S*)-Tetrahidrofur-2-il-	1 42 (d, 6H), 1 79-1 87 (m, 2H), 1 98-2 11 (m, 2H), 2 78 (s, 3H), 3 19-3 27 (m, 4H), 3 70-3 83 (m, 6H), 4 70 (dd, 1H), 4 80 (quintete, 1H), 7 23-7 30 (m, 2H), 7 59 (d, 2H), 7 98 (s, 1H), 8 74 (s, 1H), 10 02 (brs, 1H)	510
52	$MeC(Me)(OH)CH_2$-	1 19 (s, 6H), 1 42 (d, 6H), 2 50 (s, 2H), 2 79 (s, 3H), 3 25-3 33 (m, 4H), 3 81-3 89 (m, 4H), 4 80 (quintete, 1H), 7 34-7 40 (m, 2H), 7 63 (d, 2H), 7 99 (s, 1H), 8 76 (s, 1H), 10 08 (brs, 1H)	512
53	$HOCH_2C(Me)_2$-	1 18 (s, 6H), 1 42 (d, 6H), 2 79 (s, 3H), 3 25-3 29 (m, 4H), 3 44 (s, 2H), 3 84-3 90 (m, 4H), 4 80 (quintete, 1H), 7 32-7 40 (m, 2H), 7 62 (d, 2H), 7 99 (s, 1H), 8 76 (s, 1H), 10 07 (brs, 1H)	512
54	(*R*)-MeCH(Me)CH(OH)-	0 84 (d, 3H), 0 88 (d, 3H), 1 42 (d, 6H), 1 82-1 90 (m, 1H), 2 79 (s, 3H), 3 27-3 33 (m, 4H), 3 85-3 92 (m, 4H), 4 06 (d, 1H), 4 79 (quintete, 1H), 7 38-7 42 (m, 2H), 7 64 (d, 2H), 7 99 (s, 1H), 8 76 (s, 1H), 10 09 (brs, 1H)	512
55	(*S*)-MeCH(Me)CH(OH)-	0 84 (d, 3H), 0 88 (d, 3H), 1 42 (d, 6H), 1 82-1 90 (m, 1H), 2 79 (s, 3H),	512

Ej	R[1]	R[2]	R[3]	NMR	m/z	SM
10				(septuplete, 1H), 2 02 (s, 3H), 2 35 (s, 3H), 2 99 (t, 2H) 3 07 (t 2H), 3 58 (q, 4H), 4 33 (d, 2H), 6 93 (d, 2H), 7 00 (d, 1H), 7 45 (d, 2H), 7 58 (s, 1H), 8 28 (d, 1H), 9 13 (s, 1H)		de WO 03/07643 6

[1] Este compuesto requirio cromatografía posterior en oxido de aluminio neutro (actividad II) eluyendo con EtOAc DCM (1 1) luego EtOAc DCM (1 1) con 5%v/v MeOH El compuesto del titulo se cristalizo de MeOH (120 mg 25 6%)

[2] Cromatografía con MeOH DCM (2 98 a 6 94) El compuesto del titulo se cristalizó de acetonitrilo (149 mg 32 7%)

[3] Cromatografía con MeOH DCM (3 97 a 5 95) (127 mg 27%)

[4] Cromatografía con MeOH DCM (3 97) (180 mg 37%)

[5] Cromatografía con MeOH DCM (2 98 a 6 94) (290 mg 34 5%)

[6] Cromatografía con MeOH DCM (2 98 a 6 94) (340 mg 38 5%)

[7] Cromatografía con MeOH DCM (2 98 a 6 94) (350 mg 41 7%)

[8] 5-(3-Dimetilaminoprop-2-en-1-oil)-1-isopropil-2-etilimidazol (Metodo 9, 470 mg 2 mmol) y sal bicarbonato de N-[4-(4-acetilpiperazin-1-il)fenil] guanidina (Metodo 2, 740 mg 2 3mmol) en 2-metoxietanol (10 ml) se agitaron y calentaron por 24 horas a 110°C La mezcla de reaccion se evaporo bajo presión reducida y el residuo se purifico por cromatografía en gel de silice con MeOH DCM (2 98 a 6 94) Luego de la evaporacion y trituración con eter, el compuesto del título se obtuvo como un solido amarillo (290 mg 33 4%)

[9] Cromatografía con MeOH DCM (3 97 a 8 92) (186 mg 20 7%)

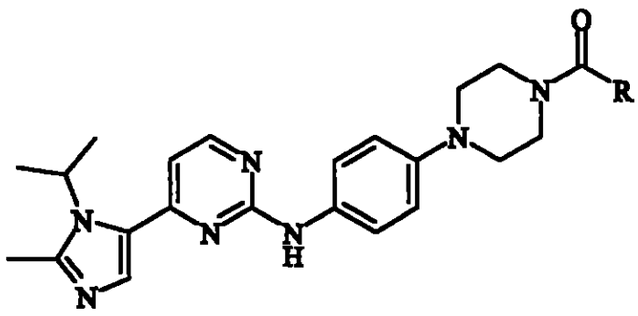
[10] Cromatografía con MeOH DCM (2 98 a 6 94) (372 mg 40%)

Ej	R	NMR	m/z
		3 27-3 33 (m, 4H), 3 85-3 92 (m, 4H), 4 06 (d, 1H), 4 79 (quintete, 1H), 7 38-7 42 (m, 2H), 7 64 (d, 2H), 7 99 (s, 1H), 8 76 (s, 1H), 10 09 (brs, 1H)	
56	$HC{\equiv}CCH_2OCH_2$-	1 42 (d, 6H), 2 78 (s, 3H), 3 22-3 30 (m, 4H), 3 49 (t, 1H), 3 67-3 75 (m, 4H), 4 23 (d, 2H), 4 26 (s, 2H), 4 80 (quintete, 1H), 7 26-7 33 (m, 2H), 7 61 (d, 2H), 7 99 (s, 1H), 8 75 (s, 1H), 10 04 (brs, 1H)	508
57	Tetrahidrofur-3-il-	1 42 (d, 6H), 2 03 (q, 2H), 2 78 (s, 3H), 3 22-3 30 (m, 4H), 3 36-3 45 (m, 1H), 3 66-3 76 (m, 4H), 3 77-3 84 (m, 4H), 4 80 (quintete, 1H), 7 28-7 36 (m, 2H), 7 61 (d, 2H), 7 99 (s, 1H), 8 75 (s, 1H), 10 05 (brs, 1H)	510
58	$(Me)_2NCH_2CH_2$-	1 42 (d, 6H), 2 74-2 78 (m, 9H), 2 93 (t, 2H), 3 21-3 32 (m, 6H), 3 72-3 78 (m, 4H), 4 80 (quintete, 1H), 7 22-7 28 (m, 2H), 7 59 (d, 2H), 7 99 (s, 1H), 8 74 (s, 1H), 10 01 (brs, 1H)	511
59	$HOCH_2N(Me)CH_2$-	1 42 (d, 6H), 2 78 (s, 3H), 2 88-2 95 (7H, m), 3 20-3 31 (m, 4H), 3 42-3 51 (m, 4H), 4 80 (quintete, 1H), 7 05 (d, 2H), 7 52 (d, 2H), 7 98 (s, 1H), 8 71 (s, 1H), 9 89 (brs, 1H)	511
60	$(HOCH_2)_2C$-	1 42 (d, 6H), 2 78 (s, 3H), 3 05-3 11 (m, 1H), 3 22-3 30 (m, 4H), 3 48-3 52 (m, 4H), 3 78-3 90 (m, 4H), 4 80 (quintete, 1H), 7 29-7 35 (m, 2H),	514

Ej	R	NMR	m/z
		7 61 (d, 2H), 7 99 (s, 1H), 8 75 (s, 1H), 10 04 (brs, 1H)	
61	Tetrazol-1-il-CH_2-	1 42 (d, 6H), 2 78 (s, 3H), 3 20-3 28 (m, 2H), 3 32-3 40 (m, 2H), 3 70-3 85 (m, 4H), 4 80 (quintete, 1H), 5 72 (s, 2H), 7 20-7 26 (m, 2H), 7 59 (d, 2H), 7 99 (s, 1H), 8 74 (s, 1H), 9 31 (s, 1H), 10 04 (brs, 1H)	522
62	1*H*-Tetrazol-5-il-CH_2-	(MeOD) 1 54 (d, 6H), 2 82 (s, 3H), 3 57-3 63 (m, 2H), 3 75-3 81 (m, 2H), 4 03-4 12 (m, 4H), 4 32 (s, 2H), 4 92 (quintete, 1H), 7 55 (d, 2H), 7 83 (d, 2H), 7 86 (s, 1H), 8 68 (s, 1H)	522
63	1 -Metil-L-prolil-	1 42 (d, 6H), 1 84-1 92 (m, 2H), 2 04-2 14 (m, 1H), 2 52-2 59 (m, 1H), 2 79-2 82 (m, 6H), 3 11-3 22 (m, 4H), 3 59-3 85 (m, 6H), 4 70-4 84 (m, 2H), 7 10 (d, 2H), 7 54 (d, 2H), 7 97 (s, 1H), 8 72 (s, 1H), 9 66 (brs, 1H), 9 93 (s, 1H)	523
64	$MeSO_2CH_2$-	1 42 (d, 6H), 2 79 (s, 3H), 3 11 (s, 3H), 3 22-3 30 (m, 4H), 3 78-3 88 (m, 4H), 4 54 (s, 2H), 4 80 (quintete, 1H), 7 23-7 27 (m, 2H), 7 59 (d, 2H), 7 98 (s, 1H), 8 74 (s, 1H), 10 02 (brs, 1H)	532

Ejemplos 65-86

Los siguientes compuestos se prepararon por el procedimiento de Ejemplo 38 usando el acido apropiado y 2-[4-(piperazin-1-il)anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina (Ejemplo 20)



Ej	R	H NMR (300MHz)	m/z
65	(R)-HOCH(Me)	($CDCl_3$) 8 31 (d, 1H), 7 46 (d, 2H), 7 38 (s, 1H), 6 92 (d, 2H), 6 86 (d, 2H), 5 66 - 5 56 (m, 1H), 4 51 (q, 1H), 3 96 - 3 72 (m, 2H), 3 64 - 3 54 (m, 2H), 3 21 - 3 10 (m, 4H), 2 72 (brs, 1H), 2 62 (s, 3H), 1 48 (d, 6H), 1 37 (d, 3H)	450
66	Ciclopropil-	9 19 (s, 1H), 8 31 (d, 1H), 7 47 (d, 2H), 7 39 (s, 1H), 6 97 (s, 1H), 6 94 (d, 2H), 5 74 - 5 65 (m, 1H), 3 88 - 3 71 (m, 2H), 3 69 - 3 54 (m, 2H), 3 17 - 2 94 (m, 4H), 2 42 (s, 3H), 2 06 -1 95 (m, 1H), 1 40 (d, 6H), 0 79 - 0 67 (m, 4H)	447
67	$MeOCH_2$-	9 18 (s, 1H), 8 33 (d, 1H), 7 49 (s, 1H), 7 47 (d, 2H), 6 96 (d, 1H)5 6 92 (d, 2H), 5 72 - 5 63 (m, 1H), 4 13 (s, 2H), 3 62 - 3 49 (m, 4H), 3 29 (s, 3H), 3 11 - 3 00 (m, 4H), 2 48 (s, 3H), 1 40 (d, 6H)	450
68	(S)-MeOCH(Me)-	9 22 (s, 1H), 8 32 (d, 1H), 7 47 (d,	464

214

Ej	R	H NMR (300MHz)	m/z
		2H), 7 43 (s, 1H), 6 93 (d, 2H), 6 95 (s, 1H), 5 73 - 5 64 (m, 1H), 4 24 (q, 1H), 3 65 (d, 4H), 3 24 (s, 3H), 3 10 (brs, 4H), 2 47 (s, 3H), 1 40 (d, 6H), 1 23 (d,3H)	
69	(S)-HOCH(Me)-	9 18 (s, 1H), 8 30 (s, 1H), 7 47 (d, 2H), 7 40 (s, 1H), 6 95 (d, 2H), 6 92 (d, 1H), 5 74 - 5 64 (m, 1H), 4 92 (d, 1H), 4 50 - 4 41 (m, 1H), 3 72 -3 50 (m, 4H), 3 13 - 2 97 (m, 4H), 2 47 (s, 3H), 1 40 (d, 6H), 1 20 (d, 3H)	450
70	(R)-MeOCH(Me)-	9 20 (s, 1H), 8 31 (d, 1H), 7 47 (d, 2H), 7 41 (s, 1H), 6 93 (d, 2H), 6 95 (s, 1H), 5 74 - 5 64 (m, 1H), 4 24 (q, 1H), 3 65 (d, 4H), 3 23 (s, 3H), 2 47 (s, 3H), 1 40 (d, 6H), 1 23 (d, 3H)	464
71	*i*-Pr-	9 21 (s, 1H), 8 31 (d, 1H), 7 47 (d, 2H), 7 40 (s, 1H), 6 94 (d, 1H), 6 92 (d, 2H), 5 74 - 5 64 (m, 1H), 3 67 (brs, 4H), 3 04 (d, 4H), 2 94 - 2 86 (m, 1H), 2 47 (s, 3H), 1 40 (d, 6H), 1 01 (d, 6H)	448
72	$MeC(Me)(OH)CH_2$-	9 19 (s, 1H), 8 30 (d, 1H), 7 47 (d, 2H), 7 38 (d, 1H), 6 94 (d, 1H), 6 92 (d, 2H), 5 74 - 5 64 (m, 1H), 4 80 (s, 2H), 3 68 - 3 59 (m, 4H), 3 29 (s, 1H), 3 10 - 2 98 (m, 4H), 2 47 (s, 3H), 1 39 (d, 6H), 1 20 (s, 6H)	478
73	2-(R)-Tetrahidrofur-2-ilo	9 20 (s, 1H), 8 31 (d, 1H), 7 47 (d, 2H), 7 42 (s, 1H), 6 94 (d, 1H), 6 92	476

Ej	R	H NMR (300MHz)	m/z
		(d, 2H), 5 73 - 5 64 (m, 1H), 4 69 (t, 1H), 3 81 - 3 70 (m, 2H), 3 69 -3 55 (m, 4H), 3 10 - 2 98 (m, 4H), 2 48 (s, 3H), 2 10 - 1 93 (m, 2H), 1 90 - 1 76 (m, 2H), 1 40 (d, 6H)	
74	2-(S)-Tetrahidrofur-2-ilo	9 20 (s, 1H) 8 32 (d, 1H), 7 47 (d, 2H), 7 42 (s, 1H), 6 94 (d, 1H), 6 92 (d, 2H), 5 73 - 5 64 (m, 1H), 4 69 (t, 1H), 3 82 - 3 70 (m, 2H), 3 69 - 3 55 (m, 4H), 3 10 - 2 99 (m, 4H), 2 48 (s, 3H), 2 09 -1 98 (m, 2H), 1 90 - 1 77 (m, 2H), 1 40 (d, 6H)	476
75[1]	1-Hidroxiciclоprop-1-ilo	9 95 (s, 1H), 8 62 (d, 1H), 8 22 (s, 1H), 7 76 -7 57 (m, 4H), 7 18 (d, 1H), 5 64 - 5 55 (m, 1H), 4 24 - 3 87 (m, 4H), 3 51 (s, 4H), 2 82 (s, 3H), 1 50 (d, 7H), 1 04 - 0 97 (m, 2H), 0 83 - 0 77 (m, 2H)	462
76[1]	(S)-$MeCH_2CH(OH)$-	9 83 (s, 1H), 8 60 (d, 1H), 8 20 (s, 1H), 7 65 (d, 2H), 7 50 (s, 2H), 7 15 (d, 1H), 5 64 - 5 54 (m, 2H), 4 97 (s, 1H), 4 25 (q, 1H), 3 99 - 3 70 (m, 4H), 3 42 - 3 25 (m, 4H), 2 81 (s, 3H), 1 72 -1 58 (m, 2H), 1 49 (d, 6H), 0 89 (t, 3H)	464
77[1]	(R)-$MeCH_2CH(OH)$-	9 90 (s, 1H), 8 61 (d, 1H), 8 21 (s, 1H), 7 68 (d, 2H), 7 50 (d, 2H), 7 16 (d, 1H), 5 64 - 5 55 (m, 1H), 4 25 (q, 1H), 4 02 - 3 73 (m, 4H), 3 45 -3 30 (m, 4H), 2 80 (s, 3H), 1 72 -1 57 (m,	464

Ej	R	H NMR (300MHz)	m/z
		2H), 1 49 (d, 6H), 0 89 (t, 3H)	
78[1]	1 -Cianocicloprop-1-ilo	9 74 (s, 1H), 8 58 (d, 1H), 8 20 (s, 1H), 7 58 (d, 2H), 7 26 (d, 2H), 7 12 (d, 1H), 5 64 - 5 55 (m, 1H), 4 97 (brs, 1H), 4 00 - 3 76 (m, 4H), 3 36 - 3 25 (m, 4H), 2 80 (s, 3H), 1 65 -1 53 (m, 4H), 1 48 (d, 6H)	471
79[1]	(R)-MeCH(Me)CH(OH)-	9 98 (s, 1H), 8 62 (d, 1H), 8 23 (s, 1H), 7 71 (d, 2H), 7 58 (d, 2H), 7 18 (d, 1H), 5 64 - 5 55 (m, 1H), 5 38 (s, 2H), 4 07 (d, 1H), 4 04 - 3 78 (m, 4H), 3 48 - 3 35 (m, 4H), 2 82 (s, 3H), 1 94 -1 82 (m, 1H), 1 50 (d, 6H), 0 87 (dd, 6H)	478
80[1]	(S)-MeCH(Me)CH(OH)-	9 87 (s, 1H), 8 60 (d, 1H), 8 21 (s, 1H), 7 64 (d, 2H), 7 47 - 7 34 (m, 2H), 7 15 (d, 1H), 5 64 -5 54 (m, 1H), 4 20 (brs, 2H), 4 08 (d, 1H), 3 98 - 3 70 (m, 4H), 3 38 - 3 25 (m, 4H), 2 81 (s, 3H), 1 93 -1 82 (m, 1H), 1 49 (d, 6H), 0 88 (d, 3H), 0 85 (d, 3H)	478
81[1]	$MeOCH_2CH_2$-	10 04 (s, 1H), 8 62 (d, 1H), 8 24 (s, 1H), 7 20 (d, 1H), 5 66 - 5 56 (m, 1H), 4 80 (brs, 1H), 4 02 (s, 4H), 3 58 (t, 2H), 3 52 (s, 4H), 3 26 (s, 3H), 2 84 (s, 3H), 2 65 (t, 2H), 1 50 (d, 6H)	464
82[1]	$HOCH_2C(Me)_2$-	9 98 (s, 1H), 8 62 (d, 1H), 8 22 (s, 1H), 7 79 -7 60 (m, 4H), 7 19 (d, 1H), 5 64 - 5 55 (m, 2H), 5 22 (s, 1H), 4 08	478

Ej	R	H NMR (300MHz)	m/z
		- 3 90 (m, 4H), 3 48 (s, 2H), 3 46 - 3 38 (m, 4H), 2 82 (s, 3H), 1 50 (d, 6H), 1 20 (s, 6H)	
83[1]	F_2CH-	9 73 (s, 1H), 8 57 (d, 1H), 8 20 (s, 1H), 7 57 (d, 2H), 7 22 (d, 2H), 7 12 (d, 1H), 6 79 (t, 1H), 5 64 - 5 55 (m, 1H), 4 69 (s, 1H), 3 83 - 3 71 (m, 4H), 3 34 - 3 21 (m, 4H), 2 80 (s, 3H), 1 47 (d, 6H)	456
84[1]	$HC{\equiv}CCH_2OCH_2$-	9 89 (s, 1H), 8 60 (d, 1H), 8 23 (s, 1H), 7 67 (d, 2H), 7 55 - 7 41 (m, 2H), 7 16 (d, 1H), 5 64 -5 55 (m, 1H), 4 60 (s, 1H), 4 29 (s, 2H), 4 24 (d, 2H), 3 49 (t, 1H), 2 81 (s, 3H), 1 50 (s, 6H)	474
85[1]	$HOC(Me)_2$-	9 24 (brs, 1H), 8 55 (d, 1H), 7 54 (d, 2H), 7 19 -7 13 (m, 2H), 7 09 (d, 1H), 5 63 - 5 54 (m, 1H), 4 84 (brs, 1H), 3 97 (s, 4H), 3 24 (s, 4H), 2 81 (s, 3H), 1 52 (d, 6H), 1 41 (s, 6H)	464
86[1]	Et-	9 89 (s, 1H), 8 61 (d, 1H), 8 21 (s, 1H), 7 68 (d, 2H), 7 57 (s, 2H), 7 16 (d, 1H), 5 64 - 5 54 (m, 1H), 4 86 (s, 1H), 3 90 (s, 4H), 3 44 - 3 30 (m, 4H), 2 81 (s, 3H), 2 39 (q, 2H), 1 49 (d, 6H), 1 01 (t, 3H)	471

[1] La base libre aislada se disolvio en EtOAc (3ml) con la adicion de unas cuantas gotas de MeOH para contribuir a la disolucion Se agrego 1 0M de cloruro de hidrogeno en solución de eter (1 equivalente), y las sales

clorhidrato resultantes se trituraron con eter, luego se filtraron y se secaron *in vacuo*

Ejemplo 87

2-{4-[4-(Acetil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina

Una solución de (2Z)-3-(dimetilamino)-2-fluoro-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona (Metodo 14, 6 0g, 25mmol) y sal bicarbonato de *N*-[4-(4-acetilpiperazin-1-il)fenil]guanidina (Metodo 2, 12 12g, 37 5mmol) en 2-metoxietanol (90mol) se calento bajo reflujo por 18 horas La mezcla de reaccion se evaporó bajo presión reducida y el compuesto del titulo se aisló por MPLC en gel de sílice (3% MeOH/DCM) Se obtuvo como una espuma crujiente con la evaporacion Rendimiento = 8 9g (81%) NMR 1 36 (d, 6H), 2 03 (s, 3H), [2 5 (s, 3H) bajo señal DMSO], 2 98 (m, 2H), 3 08 (m, 2H), 3 57 (m, 4H), 5 44 (septuplete, 1H), 6 90 (d, 2H), 7 34 (d, 1H), 7 42 (d, 2H), 8 44 (d, 1H), 9 24 (s, 1H), m/z 438

Ejemplo 88

2-[4-(Piperazin-1-il)anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina clorhidrato

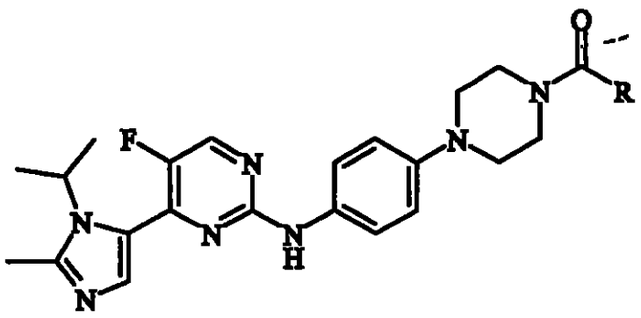
El compuesto del título se preparo de 2-{4-[4-(acetil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina (Ejemplo 87) por el procedimiento de Ejemplo 20) El compuesto del titulo cristalizo de la mezcla de reaccion como la sal HCl t se extrajo por filtracion, se lavo con isopropanol y eter Rendimiento = 8 01g (98%) NMR 1 46 (d, 6H), 2 78 (s, 3H), 3 21 (brs, 4H), 3 32 (m, 4H), 5 24 (septuplete, 1H), 6 96 (d, 2H), 7 47 (d, 1H), 8 05 (d, 2H), 8 70 (d, 1H), 9 42 (brs, 1H), 9 65 (s, 1H), m/z 396

Ejemplos 89-102

Los siguientes compuestos se prepararon por el procedimiento de Ejemplo 38 usando el acido apropiado y 2-[4-(piperazin-1-il)anilino]-4-(1-

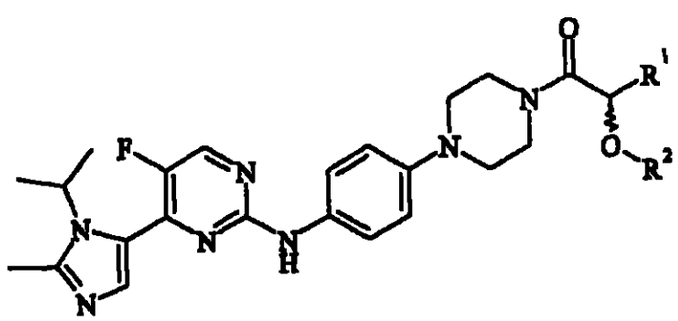
isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina clorhidrato (Ejemplo 88)

Para los Ejemplos 89-96, las bases aisladas libres se disolvieron en EtOAc (3ml) con la adición de unas cuantas gotas de MeOH para contribuir a la disolucion Se agregó 1 0M de cloruro de hidrogeno en solucion de eter (1 equivalente), y las sales clorhidrato resultantes se trituraron con eter, luego se filtraron y se secaron *in vacuo*



Ej	R	NMR ($CDCl_3$)	m/z
89	Et-	1 01 (t, 3H), 1 46 (d, 6H), 2 38 (q, 2H) 2 80 (s, 3H) 3 23-3 33 (m 4H), 3 73-3 81 (m, 4H), 5 25 (quintete, 1H), 7 32-7 40 (m, 2H), 7 61 (d, 2H), 8 07 (d, 1H), 8 75 (d, 1H) 9 85 (brs, 1H)	452
90	$HOCH_2CH_2$-	1 46 (d, 6H), 2 53 (t, 2H), 2 78 (s, 3H), 3 10-3 17 (m, 4H), 3 62-3 68 (m, 4H), 3 70 (t, 2H), 5.28 (quintete, 1H) 6 97 (d, 2H), 7 44 (d, 2H), 7 90 (d, 1H), 8 60 (d, 1H) 9 18 (brs, 1H)	468
91	$MeOCH_2CH_2$-	1 45 (d, 6H), 2 62 (t, 2H), 2 79 (s, 3H), 3 14-3 22 (m, 4H), 3 23 (s, 3H), 3 57 (t, 2H), 33 69-3 77 (m, 4H), 5 25 (quintete, 1H), 7 18-2.26 (m 2H), 7 55 (d, 2H), 8 06 (d, 1H), 8 73 (d, 1H), 9 76 (brs, 1H)	482
92	$MeOCH_2$-	1 47 (d, 6H), 2 80 (s, 3H), 3 30 (s, 3H),	468

Ej	R	NMR ($CDCl_3$)	m/z
		3 31-3 38 (m, 4H), 3 73-3 82 (m 4H), 4 15 (s, 2H), 5 24 (quintete, 1H), 7 40-7 47 (m, 2H), 7 63 (d, 2H), 8 08 (d 1H), 8 76 (d, 1H), 9 90 (brs, 1H)	
93	*i*-Pr-	1 01 (d, 6H), 1 45 (d, 6H), 2 75 (s 3H), 2 90 (quintete, 1H), 3 10-3 18 (m, 4H), 3 66-3 74 (m, 4H), 5 25 (quintete 1H), 7 08-7 16 (m, 2H), 7 51 (d, 2H) 8 06 (d, 1H), 8 72 (d, 1H), 9 69 (brs, 1H)	466
94	(*R*)-MeCH(OH)-	1 10 (d, 3H), 1 45 (d, 6H), 2 79 (s, 3H) 3 20-3 33 (m, 4H), 3 75-3 87 (m, 4H), 4 47 (q, 1H), 5 25 (quintete, 1H), 7 27-7 33 (m, 2H), 7 57 (d, 2H), 8 07 (d, 1H), 8 73 (d, 1H), 9 81 (brs, 1H)	468
95	MeC(Me)(OH)-'	1 34 (s, 36H), 1 47 (d, 6H), 2 80 (s, 3H), 3 34-3 41 (m, 4H), 3 80-4 00 (m, 4H), 5 24 (quintete, 1H), 7 47-7 55 (m, 2H), 7 65 (d, 2H), 8 08 (d, 1H), 8 77 (d, 1H) 9 92 (brs, 1H)	482
96	(S)-MeCH(OH)-	1 21 (d, 3H), 1 48 (d, 6H), 2 78 (s, 3H), 3 15 (b s, 4H), 3 74 (b s, 4H), 4 46 (q, 1H), 5 27 (septuplete, 1H), 7 90 (b s, 2H) 7 50 (b d, 2H), 8 09 (d, 1H), 8 72 (d, 1H), 9 57 (b s, 1H)	468



Ej	R^1	R^2	*forma*	NMR ($CDCl_3$)	^{19}F NMR	m/z
97	Et	H	R	1 02 (t, 3H), 1 47 (d 6H), 1 55 (m, 1H), 1 75 (m, 1H), 2 59 (s, 3H), 3 15 (m, 4H), 3 58 (brs, 2H), 3 69 (d 1H), 3 80 (m, 1H), 3 88 (m 1H) 4 36 (m 1H), 5 54 (septuplete, 1H), 6 80 (s, 1H), 6 92 (d, 2H), 7 40 (d, 2H), 7 57 (d, 1H) 8 23 (d, 1H)	-147 82	482
98	Me	Me	*R*	1 42 (d, 3H), 1 47 (d, 6H), 2 59 (s, 3H), 3 15 (m, 4H) 3 38 (s, 3H), 3 80 (m, 4H), 4 20 (q, 1H), 5 54 (septuplete, 1H), 6 80 (s, 1H), 6 92 (d, 2H), 7 40 (d, 2H), 7 57 (d, 1H), 8 23 (d, 1H)	-147 93	482
99[1]	i-*Pr*	H	*R*	0 83 (d, 3H), 1 10 (d 3H), 1 47 (d, 6H), 1 55 (m, 1H), 1 87 (septuplete, 1H), 2 59 (s, 3H), 3 13 (m, 4H), 3 58 (m, 3H), 3 69 (d, 1H), 3 80 (m, 1H), 3 88 (m, 1H), 4 28 (dd 1H), 5 54 (septuplete, 1H), 6 80 (s, 1H) 6 91 (d, 2H), 7 40 (d, 2H), 7 57 (d, 1H), 8 23 (d, 1H)	147 82	496
100	Et	H	*S*	1 02 (t, 3H), 1 47 (d, 6H), 1 55 (m, 1H), 1 75 (m, 1H) 2 59 (s, 3H), 3 15 (m, 4H), 3 58 (brs 2H) 3 69 (d, 1H), 3 80 (m 1H), 3 88 (m, 1H), 4 36 (m, 1H), 5 54 (septuplete, 1H), 6 80 (s, 1H), 6 92 (d, 2H), 7 40 (d, 2H), 7 57 (d, 1H), 8 23 (d, 1H)	-147 82	482

Ej	R[1]	R[2]	*forma*	NMR ($CDCl_3$)	^{19}F NMR	m/z
101	Me	Me	*S*	1 42 (d, 3H), 1 47 (d, 6H), 2 59 (s, 3H), 3 15 (m, 4H), 3 38 (s 3H), 3 80 (m, 4H), 4 20 (q, 1H) 5 54 (septuplete, 1H), 6 80 (s, 1H) 6 92 (d, 2H), 7 40 (d, 2H), 7 57 (d, 1H), 8 23 (d, 1H)	-147 93	482
102[2]	i-*Pr*	H	*S*	0 83 (d, 3H) 1 10 (d, 3H) 1 47 (d, 6H), 1 55 (m, 1H), 1 87 (septuplete, 1H), 2 59 (s, 3H), 3 13 (m, 4H) 3 58 (m, 3H), 3 69 (d, 1H), 3 80 (m, 1H), 3 88 (m, 1H), 4 28 (dd, 1H) 5 54 (septuplete, 1H), 6 80 (s, 1H), 6 91 (d, 2H), 7 40 (d, 2H), 7 57 (d, 1H), 8 23 (d, 1H)	-147 82	496

[1] Cromatografía con 5% MeOH NH_3 (7N) en solución DCM EtOAc (1 1)

[2] Compuesto requirio cromatografía adicional eluyendo con 5% MeOH en EtOAc

Ejemplo 103

2-{4-[4-(2-Acetoxiacetil)piperazin-1-il]anilin}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina

Los compuestos del título se prepararon usando el procedimiento de Ejemplo 21 empleando 2-[4-(piperazin-1-il)anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina clorhidrato (Ejemplo 88, 200mg 0 5 mmol) Luego del desarrollo, la mezcla se purifico por cromatografía en gel de silice usando MeOH DCM (3 97 a 6 94) para producir un solido 170 mg M/z 496

Ejemplo 104

2-{4-[4-(2-Hidroxiacetil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina clorhidrato

2-{4-[4-(2-Acetoxiacetil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina (Ejemplo 103) se desprotegio por el procedimiento de Ejemplo 22 La mezcla de reaccion se evaporo bajo presión reducida El residuo se disolvió en DCM (15 ml), se lavó con agua (10ml) y salmuera (10ml), se seco y se evaporo El residuo se trituro con eter y se re-evaporo para producir el compuesto del titulo como un sólido 134 mg Este se convirtio en la sal clorhidrato de EtOH por la adicion de 1M éter / HCl Luego de la evaporación y trituración con eter, se obtuvo un sólido NMR 1 46 (d, 6H), 2 78 (s, 3H), 3 14 (b s, 4H), 3 58 (b s, 2H), 3 68 (b s, 2H), 4 13 (s, 2H), 5 26 (septuplete, 1H), 7 10 (b s, 2H), 7 50 (d, 2H), 8 08 (d, 1H), 8 72 (d, 1H), 9 68 (b s, 1H), m/z 454

Ejemplo 105

2-{-4-[4-(Acetil)piperazin-1-il]anilino}-4-(1-ciclobutil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina

El compuesto del titulo se preparó de (2*Z*)-1-(1-ciclobutil-2-metil-1*H*-imidazol-5-il)-3-(dimetilamino)-2-fluoroprop-2-en-1-ona (Metodo 16, 1 406g) y sal bicarbonato de *N*-[4-(4-acetilpiperazin-1-il)fenil]guanidina (Método 2, 2 71g) por el procedimiento de Ejemplo 18 para producir un solido blanco (2 21g, 88%) NMR 1 61-1 72 (m, 2H), 2 06 (s, 3H), 2 30-2 43 (m, 4H), 2 75 (s, 3H), 3 27-3 39 (m, 4H), 3 77-3 85 (m, 4H), 5 22 (quintete, 1H), 7 42- 7 48 (m, 2H), 7 69 (d, 2H), 8 09 (d, 1H), 8 74 (d, 1H), 9 97 (brs, 1H), m/z 450

Ejemplo 106

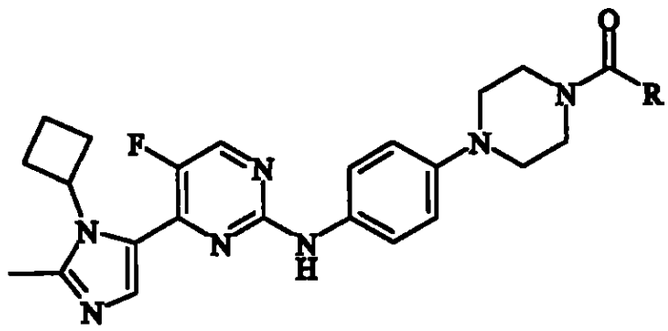
2-[4-(Piperazin-1-il)anilino]-4-(1-ciclobutil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina

El compuesto del titulo se preparo de 2-{4-[4-(acetil)piperazin-1-il]anilino}-4-(1-ciclobutil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina

(Ejemplo 105, 1 89g) por el procedimiento de Ejemplo 20 para producir un sólido amarillo (1 538g, 90%) NMR ($CDCl_3$) 1 61-1 78 (m, 2H), 2 35-2 45 (m, 4H), 2 59 (s, 3H), 3 03-3 09 (m, 4H), 3 10-3 15 (m, 4H), 5 33 (quintete, 1H), 6 93 (s, 1H), 6 95 (d, 2H), 7 42 (d, 2H), 7 49 (d, 1H), 8 22 (d, 1H), m/z 408

Ejemplos 107-110

Los siguientes compuestos se prepararon por el procedimiento de Ejemplo 38 usando el acido apropiado y 2-[4-(piperazin-1-il)anilino]-4-(1-ciclobutil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina (Ejemplo 106) Las bases aisladas libres se disolvieron en EtOAc (3ml) con la adicion de unas cuantas gotas de MeOH para contribuir a la disolucion Se agrego 1 0M de cloruro de hidrógeno en solucion de éter (1 equivalente), y las sales clorhidrato resultantes se trituraron con éter, luego se filtraron y se secaron *in vacuo*



Ej	R	NMR (300MHz, $CDCl_3$)	m/z
107	$HOCH_2$-	1 61-1 72 (m, 2H), 2 31-2 44 (m, 4H), 2 75 (s, 3H), 3 28-3 36 (m, 4H), 3 70-3 85 (m, 4H), 4 15 (s, 2H), 5 22 (quintete, 1H), 7 42 (m, 2H, 7 68 (d, 2H), 8 09 (s, 1H), 8 74 (1H, s), 9 95 (brs, 1H)	466
108	(*S*)-MeCH(OH)-	1 22 (d, 3H), 1 63-1 72 (m, 2H), 2 30-2 43 (m, 4H), 2 75 (s, 3H), 3 30-3 38 (m, 4H), 3 80-3 96 (m, 4H), 4 46 (q, 1H), 5 22 (quintete, 1H), 7 39-7 47 (m, 2H),	480

Ej	R	NMR (300MHz, $CDCl_3$)	m/z
		7 68 (d, 2H), 8 08 (d, 1H), 8 74 (d, 1H), 9 95 (brs, 1H)	
109	(*R*)-MeCH(OH)-	1 22 (d, 3H), 1 63-1 72 (m, 2H), 2 30-2 43 (m, 4H), 2 75 (s, 3H), 3 30-3 38 (m, 4H), 3 80-3 96 (m, 4H), 4 46 (q, 1H), 5 22 (quintete, 1H), 7 39-7 47 (m, 2H), 7 68 (d, 2H), 8 08 (d, 1H), 8 74 (d, 1H), 9 95 (brs, 1H)	480
110	$MeOCH_2$-	1 62-1 72 (m, 2H), 2 30-2 44 (m, 4H), 2 75 (s, 3H), 3 31 (s, 3H), 3 32-3 39 (m, 4H), 3 75-3 85 (m, 4H), 4 16 (s, 2H), 5 22 (quintete, 1H), 7 43-7 50 (m, 2H), 7 70 (d, 2H), 8 09 (d, 1H), 8 75 (d, 1H), 9 99 (brs, 1H)	480

Ejemplo 111

2-[4-(Morfolino)anilin]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina

(2*E*)-3-(Dimetilamino)-1-(1-isopropil-2-metil-1*H*-imidazol-5-il) prop-2-en-1-ona (Método 24 de WO 03/076436), (110mg 0 5mmol) y sal bicarbonato de *N*-[4-(morfolino)fenil]guanidina (Metodo 4, 170mg 0 6mmol) en dimetilacetamida (4ml) se calentaron por 20 minutos a 200°C en un microondas La mezcla de reaccion se evaporo bajo presion reducida y el residuo se purificó por cromatografía en gel de silice con MeOH DCM (4 96 a 8 92) para producir el compuesto del titulo, luego de trituracion con eter, como un solido 90mg 50% NMR 1 42 (d, 6H), 2 48 (s, 3H), 3 06 (t, 4H), 3 75 (t, 4H), 5 71 (septuplete, 1H), 6 91 (d, 2H), 6 97 (d, 1H), 7 40 (s, 1H), 7 48 (d, 2H), 8 32 (s, 1H), 9 18 (s, 1H), m/z 379

Ejemplo 112

2-[4-(Morfolino)anilino]-4-(1-etil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina clorhidrato

(2*E*)-3-(Dimetilamino)-1-(1-etil-2-metil-1*H*-imidazol-5-il)-2-fluoro-prop-2-en-1-ona (Metodo 15, 250mg 1 11mmol) y sal bicarbonato de *N*-[4-(morfolino)fenil]guanidina (Método 4, 405mg 1 44mmol) en 2-metoxietanol (4 5ml) se calentaron por 30 minutos a 200°C en un microondas La mezcla de reacción se evaporo bajo presión reducida y el residuo se purifico por cromatografía en oxido de aluminio neutro (actividad II) con MeOH DCM EtOAc (1 79 5 19 5) para producir el compuesto del titulo, luego de trituración con éter, como un solido 230mg 54% Éste se convirtió en la sal clorhidrato de MeOH con 1M éter/HCl La trituración con eter y la evaporación produjo el compuesto del titulo como un solido NMR 1 19 (t, 3H), 2 70 (s, 3H), 3 12 (b s, 4H), 3 60 (b s, intercambiables), 3 79 (t, 4H), 4 59 (q, 2H), 7 05 (b s, 2H), 7 44 (d, 2H), 8 20 (d, 1H), 8 68 (d, 1H), 9 54 (s, 1H), m/z 383

Ejemplo 113

2-[4-(Morfolino)anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina

(2*E*)-3-(Dimetilamino)-2-fluoro-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona (Método 14, 240mg 1 0mmol) y sal bicarbonato de *N*-[4-(morfolino)fenil]guanidina (Metodo 4, 367mg 1 3mmol) en 2-metoxietanol (4 5ml) se calentaron por 40 minutos a 160°C, luego 20 minutos a 180°C en un microondas La mezcla de reaccion se evaporo bajo presión reducida y el residuo se purificó por cromatografía en gel de silice con MeOH DCM EtOAc (4 48 48 a 10 45 45) para producir el compuesto del titulo como un sólido 180mg 45% Este se convirtió en la sal clorhidrato de MeOH con 1M eter/HCl La trituracion con eter y la evaporacion produjo el compuesto del título como un sólido NMR (373K) 1 48 (d, 6H), 2 77 (s, 3H), 3 09 (t, 4H), 3 78 (t, 4H), 5 30 (septuplete, 1H), 6 94 (d, 2H), 7 43 (d, 2H), 7 88 (d, 1H), 8 602 (d, 1H), m/z 397

Ejemplo 114

2-[4-(Morfolino)anilino]-4-(1-ciclobutil-2-metil-1*H*-imidazol-5-il) pirimidina

El compuesto del titulo se preparo de (2*E*)-1-(1-ciclobutil-2-metil-1*H*-imidazol-5-il)-3-(dimetilamino)prop-2-en-1-ona (Metodo 37 de WO 03/076435, 233mg) y *N*-(4-morfolin-4-ilfenil)guanidina (Metodo 4, 405mg) por el procedimiento de Ejemplo 111 para producir un sólido blanco (228mg, 61%) NMR 1 59-1 72 (m, 2H), 2 32-2 44 (m, 4H), 2 75 (s, 3H), 3 21-3 28 (m, 4H), 3 84-3 92 (m, 4H), 5 40 (quintete, 1H), 7 09 (d, 1H), 7 24-7 32 (m, 2H), 7 66 (d, 2H), 8 11 (s, 1H), 8 57 (d, 1H), 9 77 (brs, 1H), m/z 391

Ejemplo 115

2-[4-(Morfolino)anilino]-4-(1-ciclobutil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina

El compuesto del titulo se preparo de (2*Z*)-1-(1-ciclobutil-2-metil-1*H*-imidazol-5-il)-3-(dimetilamino)-2-fluoroprop-2-en-1-ona (Método 16, 234mg) y *N*-(4-morfolin-4-ilfenil)guanidina (Metodo 4, 410mg) por el procedimiento de Ejemplo 111 para producir un solido blanco (288 mg, 76%) NMR 1 61-1 72 (m, 2H), 2 29-2 45 (m, 4H), 2 75 (s, 3H), 3 26-3 34 (m, 4H), 3 90-3 97 (m, 4H), 5 22 (quintete, 1H), 7 38-7 45 (m, 2H), 7 68 (d, 2H), 8 08 (d, 1H), 8 73 (d, 1H), 9 95 (brs, 1H), m/z 409

Ejemplo 116

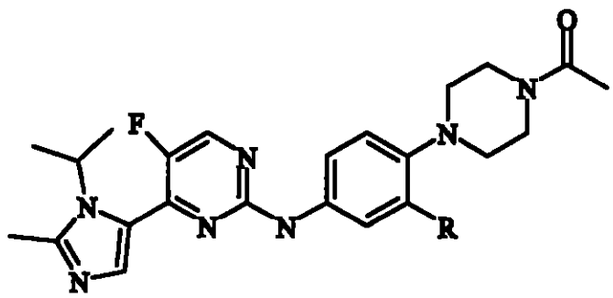
2-{4-[4-(Acetil)piperazin-1-il]3-metilanilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina

Una solucion de (2*Z*)-3-(dimetilamino)-2-fluoro-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona (Metodo 14, 1 53g, 6 4mmol) y sal bicarbonato de *N*-[4-(4-acetilpiperazin-1-il)3-metilfenil]guanidina (Metodo 31, 3 23g, 9 60mmol) en 2-metoxietanol (10ml) se calento bajo reflujo por 24 horas La mezcla de reaccion se evaporo bajo presión reducida y el

residuo se purifico por cromatografía en gel de silice con MeOH DCM EtOAc (1 49 5 49 5 a 10 45 45) para producir un solido, el cual requirio purificación posterior con MeOH DCM (1 99 a 10 90) Luego de trituracion con éter y evaporacion del disolvente, el compuesto del titulo se obtuvo como una espuma crujiente, la cual se seco en un horno de vacio de un dia para otro a 50°C (1 91g, 66%) NMR (400MHz) 1 40 (d, 6H), 2 05 (s, 3H), 2 26 (s, 3H), 2 55 (s, 3H, bajo señal de DMSO), 2 77 (dt, 4H), 3 58 (m, 4H), 5 41 (septete, 1H), 6 98 (d, 1H), 7 34 (d, 1H), 7 35 (d, 1H), 7 42 (dd, 1H), 8 49 (d, 1H), 9 28 (s, 1H), ^{19}F NMR (400MHz)-149 40 (t, 1^{F}), m/z 452

Ejemplo 117-118

Los siguientes compuestos se prepararon usando el procedimiento de Ejemplo 116 de (2*Z*)-3-(dimetilamino)-2-fluoro-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona (Metodo 14) y la guanidina apropiada



Ej	R	NMR (400MHz)	m/z	SM
117[1]	Cl	1 43 (d, 6H), 2 05 (s, 3H), 2 51 (s, 3H, bajo señal DMSO), 2 89 (dt, 4H), 3 59 (m, 4H), 5 37 (septete, 1H), 7 12 (d, 1H), 7 36 (d, 1H), 7 53 (dd, 1H), 7 77 (d, 1H), 8 55 (d, 1H), 9 54 (s, 1H), ^{19}F NMR (400MHz)-148 33 (t, 1F)	472-474	Metodo 32
118[2]	F	118 F 1 44 (d, 6H), 2 04 (s, 3H), 2 57 (s, 3H, bajo señal DMSO), 2 92 (dt, 4H), 3 58 (m, 4H), 5 42 (septete, 1H), 7 00 (t, 1H),	456	Metodo 33

Ej	R	NMR (400MHz)	m/z	SM
		7 30 (dd, 1H), 7 36 (d, 1H), 7 58 (dd, 1H), 8 55 (d, 1H), 9 55 (s, 1H), ^{19}F NMR (400 MHz)-148 47 (t, 1F)		

[1] Cromatografía con MeOH DCM EtOAc(1 49 5 49 5 a 10 45 45) (469 8 mg, 69%)

[2] Cromatografía con MeOH DCM EtOAc (1 49 5 49 5 a 10 45 45) (2 72g, 72%)

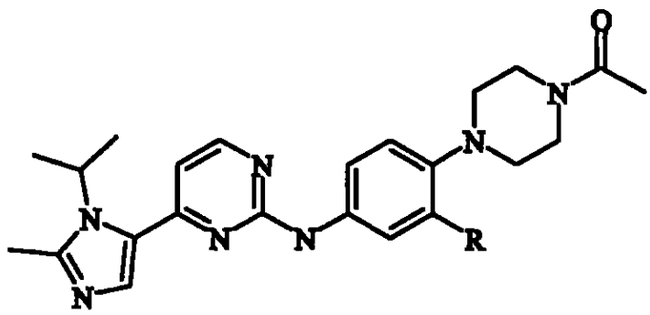
Ejemplo 119

2-{4-[4-(Acetil)piperazin-1-il]3-metilanilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina

El compuesto del titulo se preparo de (2*E*)-3-(dimetilamino)-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona (Metodo 24 de WO 03/076436, 331 8g, 1 5mmol) y sal bicarbonato de *N*-[4-(4-acetilpiperazin-1-il)3-metilfenil]guanidina (Método 31, 758 3mg, 2 25mmol) por el procedimiento de Ejemplo 116 La mezcla de reaccion se evaporo bajo presion reducida y el residuo se purifico por cromatografía en gel de silice con MeOH DCM EtOAc (1 49 5 49 5 a 10 45 45) para producir un solido (419 4mg, 65%) NMR 1 41 (d, 6H), 2 05 (s, 3H), 2 27 (s, 3H), 2 48 (s, 3H), 2 77 (dt, 4H), 3 58 (m, 4H), 5 66 (septete, 1H), 6 97 (d, 1H), 6 99 (d, 1H), 7 37 (d, 1H), 7 41 (s, 1H), 7 47 (dd, 1H), 8 35 (d, 1H), 9 20 (s, 1H), m/z 434

Ejemplos 120-121

Los siguientes compuestos se prepararon usando el procedimiento de Ejemplo 119 de (2*E*)-3-(dimetilamino)-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona (Metodo 24 de WO 03/076436) y la guanidina apropiada



Ej	R	NMR (400MHz)	m/z	SM
120[1]	Cl	1 45 (d, 6H), 2 05 (s, 3H), 2 50 (s, 3H+DMSO), 2 90 (dt, 4H), 3 59 (m, 4H), 5 62 (septete, 1H), 7 05 (d, 1H), 7 12 (d, 1H), 7 43 (s, 1H), 7 57 (dd, 1H), 7 81 (d, 1H), 8 40 (d, 1H), 9 45 (s, 1H)	454-456	Metodo 32
121[2]	F	1 45 (d, 6H), 2 04 (s, 3H), 2 57 (s, 3H+DMSO), 2 93 (dt, 4H), 3 59 (m, 4H), 5 68 (septete, 1H), 7 00 (t, 2H), 7 05 (d, 2H), 7 33 (dd, 1H), 7 42 (s, 1H), 7 64 (dd, 1H), 8 39 (d, 1H), 9 46 (s, 1H)	438	Metodo 33

[1] Este compuesto requirió cromatografía posterior en HPLC preparativa Basica con acetonitrilo 1% NH_3 / H_2O (25 75 a 70 30) (475 mg, 52%)

[2] (413 5mg, 63%)

Ejemplo 122

2-[4-(Piperazin-1-il)3-metilanilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)fluoropirimidina

2-{4-[4-(Acetil)piperazin-1-il]3-metilanilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina (Ejemplo 116, 1 89g, 4 19mmol) se agito y se calento en isopropanol (20ml), H_2O (5ml) y 33% de acido clorhidrico (4ml) a 90°C por 10 horas El disolvente se evaporó bajo presión reducida para producir un residuo el cual se repartio en porciones entre agua y DCM, se basifico con bicarbonato de sodio saturado y la capa acuosa se extrajo con DCM dos veces Los organicos se combinaron, se lavaron con salmuera, se secaron, y la evaporacion del disolvente para producir el compuesto del titulo como una espuma crujiente, la cual se seco

en un horno de vacio de un dia para otro a 50°C (1 53g, 89%) NMR (400 MHz) 1 39 (d, 6H), 2 23 (s, 3H), 2 51 (s, 3H, bajo señal DMSO), 2 72 (m, 4H), 2 85 (m, 4H), 3 29 (s, 1H bajo señal H_2O), 5 42 (septete, 1H), 6 95 (d, 1H), 7 30 (d, 1H), 7 35 (d, 1H), 7 40 (dd, 1H), 8 48 (d, 1H), 9 24 (s, 1H), ^{19}F NMR (400MHz)-149 59 (t, 1F), m/z 410

Ejemplo 123

2-[4-(Piperazin-1-il)3-fluoroanilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina

El compuesto se preparó de 2-{4-[4-(acetil)piperazin-1-il]3-fluoroanilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina (Ejemplo 118, 455mg, 1mmol) por el procedimiento de Ejemplo 122 El compuesto del titulo se obtuvo como una espuma crujiente la cual se seco en un horno de vacio de un dia para otro a 50°C (337 8mg, 82%) NMR (400 MHz) 1 41 (d, 6H), 2 23 (s, 3H), 2 50 (s, 3H, bajo señal DMSO), 2 90 (s, 8H), 3 29 (s, 1H bajo señal H_2O), 5 43 (septete, 1H), 6 96 (t, 1H), 7 29 (dd, 1H), 7 36 (d, 1H), 7 53 (dd, 1H), 8 53 (d, 1H), 9 50 (s, 1H), ^{19}F NMR (400MHz) -148 60 (t, 1F), m/z 414

Ejemplo 124

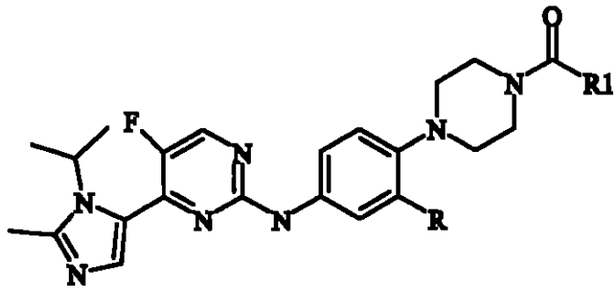
2-{4-[4-((2S)-2-Hidroxipropionil)piperazin-1-il]3-metilanilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina

Una solución de 2-[4-(piperazin-1-il)3-metilanilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina (Ejemplo 122, 490 8mg, 1 20mmol), ácido L-láctico (129 7mg, 1 44mmol), HOBt H_2O (220 5mg, 1 44mmol) y DIPEA (0 24ml, 1 44mmol) en DMF (5ml) se enfrio a 0°C, seguido por la adicion de EDAC (230 05mg, 1 44mmol) en porciones La mezcla se agito entonces a temperatura ambiente por 3 5 horas La solucion se concentro *in vacuo*, luego el residuo se repartio en porciones entre DCM y agua + bicarbonato de sodio saturado El extracto organico se lavo con agua (3 veces), salmuera, se secó y se concentro A una solucion de producto crudo en MeOH (5ml) se agregó 1 miniesfera de KOH y la mezcla

se agito a temperatura ambiente por 20 minutos El residuo obtenido con evaporacion se purificó por cromatografía en gel de silice con MeOH DCM (1 99 a 5 95) para producir el compuesto del titulo, luego de trituracion con éter, como un sólido, el cual se seco en un horno de vacio de un dia para otro a 50°C (415mg, 72%) NMR (500 MHz a 373K) 1 27 (d, 3H), 1 40 (d, 6H), 2 28 (s, 3H), 2 48 (s, 3H, bajo señal DMSO), 2 82 (m, 4H), 3 65 (m, 4H), 4 47 (m, 2H), 5 38 (septete, 1H), 7 00 (d, 1H), 7 35 (m, 2H), 7 40 (dd, 1H), 8 40 (d, 1H), 8 80 (s, 1H), ^{19}F NMR (400MHz)-149 33 (t, 1F), m/z 482

Ejemplos 125-128

Los siguientes compuestos se prepararon por el procedimiento de Ejemplo 124 usando el acido apropiado y pirimidina



Ej	R	R1	NMR (500MHz) a 373K	m/z	SM
125[1]	Me	CH_2OH	1 40 (d, 6H), 2 27 (s, 3H), 2 50 (s, 3H, bajo señal DMSO), 2 80 (m, 4H), 3 57 (m, 4H), 4 13 (d, 2H), 4 20 (t, 1H), 5 37 (septete, 1H), 6 98 (d, 1H), 7 31 (m, 2H), 7 38 (dd, 1H), 8 40 (d, 1H), 8 80 (s, 1H), ^{19}F NMR (400MHz)-149 31 (t, 1F)	468	Ejemplo 122
126[2]	F	CH_2OH	1 44 (d, 6H), 2 59 (s, 3H bajo señal DMSO), 2 94 (brs, 4H), 3 57 (brd, 4H), 4 13 (brd, 2H), 4 59 (br t, 1H), 5 43 (septete, 1H),	472	Ejemplo 123

Ej	R	R1	NMR (500MHz) a 373K	m/z	SM
			7 00 (t, 1H), 7 30 (dd, 1H), 7 36 (d, 1H), 7 58 (dd, 1H), 8 55 (d, 1H), 9 55 (s, 1H), ^{19}F NMR - 148 46 (t, 1F)		
127[3]	F	(*S*)-MeCH(OH)-	1 25 (d, 3H), 1 44 (d, 6H), 2 50 (s, 3H, bajo señal DMSO), 3 00 (m, 4H), 3 66 (m, 4H), 4 46 (m, 2H), 5 38 (septete, 1H), 6 99 (t, 1H), 7 28 (dd, 1H), 7 33 (d, 1H), 7 49 (dd, 1H), 8 44 (d, 1H), 9 09 (s, 1H), ^{19}F NMR (500MHz) -148 40 (t, 1F), -122 6 (s, 1F)	486	Ejemplo 123
128[4]	F	CH_2OMe	1 43 (d, 6H), 2 50 (s, 3H, bajo señal DMSO), 3 00 (m, 4H), 3 33 (s, 3H), 3 60 (m, 4H), 4 10 (s, 2H), 5 40 (septete, 1H), 7 00 (t, 1H), 7 30 (dd, 1H), 7 33 (d, 1H), 7 50 (dd, 1H), 8 43 (d, 1H), 9 09 (s, 1H), ^{19}F NMR (500MHz) - 148 40 (t, 1F), -122 7 (s, 1F)	486	Ejemplo 123

[1] Se agrego más acido (9mg) y EDAC (23mg) y tiempo de reaccion = 4 5 horas, (365mg, 65%)

[2] Se agrego mas ácido (10mg) y EDAC (20mg) y tiempo de reaccion = 5 5 horas, NMR (400MHz, RT) Cromatografía con MeOH DCM (1 99 a 6 94), (334 5mg, 71%)

[3] Se agregó mas ácido (10mg) y EDAC (19mg) y tiempo de reaccion = 6 horas, (378mg, 78%)

[4] No se necesito tratar el producto crudo con KOH en MeOH, (310mg, 64%)

Ejemplo 129

2-{4-[(3R,5*S*)-4-Acetil-3,5-dimetilpiperazin-1-il]anilino}-4(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina

El compuesto del titulo se preparó de (2*Z*)-3-(dimetilamino)-2-fluoro-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona (Método 14, 331mg, 1 38mmol) y *N*-[4-((3*R*,5*S*)-4-acetil-3,5-dimetilpiperazin-1-il)fenil]guanidina (Metodo 34, 737 1mg, 2 10mmol) por el procedimiento de Ejemplo 116 La mezcla de reacción se evaporo bajo presion reducida y el residuo se purificó por cromatografía en gel de silice con MeOH DCM EtOAc (1 49 5 49 5 a 10 45 45) para producir un solido, el cual se seco en un horno de vacío de un dia para otro a 50°C (485mg, 76%) NMR (400MHz) 1 30 (s, 6H), 1 41 (d, 6H), 2 05 (s, 3H), 2 50 (s, 3H bajo señal DMSO), 2 73 (m, 2H), 3 40 (d, 2H), 4 30 (brs, 2H), 5 45 (septete, 1H), 6 95 (d, 2H), 7 35 (d, 1H), 7 45 (d, 2H), 8 49 (d, 1H), 9 25 (s, 1H), ^{19}F NMR (400 MHz) -149 80 (t, 1F), m/z 466

Ejemplo 130

2-{4-[(2*S*,5*R*)-4-Acetil-2,5-dimetilpiperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina

El compuesto del titulo se preparo de (2*Z*)-3-(dimetilamino)-2-fluoro-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona (Metodo 14,335mg, 1 40mmol) y *N*-[4-((2*S*,5*R*)-4-acetil-2,5-dimetilpiperazin-2-il)fenil]guanidina (Método 35, 737 1mg, 2 10mmol) por el procedimiento de Ejemplo 116 La mezcla de reaccion se evaporo bajo presion reducida y el residuo se purifico por cromatografía en gel de silice con MeOH DCM EtOAc (1 49 5 49 5 a 6 47 47) para producir un solido, el cual requirió purificacion posterior con MeOH DCM (1 99 a 6 94) Luego de trituracion con eter y evaporación del disolvente, el compuesto del titulo se obtuvo como un solido, el cual se seco en un horno de vacio de un dia para otro a 50°C (330mg, 51%) NMR (500 MHz) 0 95 (d, 3H), 1 33 (d, 3H), 1 40 (d, 6H), 2 03 (s, 3H), 2 50 (s, 3H+DMSO), 3 17 (m, 2H), 3 43 (brs, 1H), 3 83 (brs, 1H), 4 00 (m, 1H), 4 47 (brs, 1H), 5 40 (septete, 1H), 6 83

(d, 2H), 7 32 (d, 1H), 7 37 (d, 2H), 8 35 (d, 1H), 8 7 (s, 1H), ^{19}F NMR (500 MHz MHz) -149 95 (t, 1F), m/z 466

Ejemplo 131

2-(3-Cloro-4-piperazin-1-il)anilino-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina clorhidrato

2-[3-Cloro-4-(4-acetilpiperazin-1-il)anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina (Ejemplo 120, 4 1g, 9 1mmol) se agito y se calentó en isopropanol (41ml) y 33% acido clorhidrico (4 1ml) a 85°C por 25 horas La reacción se evaporo bajo presion reducida y luego se diluyo con agua (200ml), se lavó con DCM (200ml), se basifico con solucion de bicarbonato de sodio saturado acuoso y se extrajo con cloroformo (2 x 400ml) La solucion se secó y se evaporo bajo presión reducida para producir la amina, la cual se convirtio en la sal clorhidrato disolviendo en MeOH DCM (60ml, 1 1) y tratando con una solución molar 1 0 de HCl etereo (9 1mol) El solido se trituró con eter (40ml) y se filtro para producir el compuesto del titulo (3 2g, 77%) NMR 1 42 (d, 6H), 2 61 (s, 3H), 3 16 (m, 4H), 3 40 (m, 4H), 5 58 (septete, 1H), 7 10 (d, 1H), 7 14 (d, 1H), 7 48 (dd, 1H), 7 81 (s, 2H), 8 49 (d, 1H), 9 64 (s, 1H), m/z 412

Ejemplo 132

2-[3-Cloro-4-(hidroxiacetil)piperazin-1-il]anilino-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina

A una solución de 2-(3-cloro-4-piperazin-1-il)anilino-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina clorhidrato (Ejemplo 131, 0 44g, 1 0mmol) en DCM DMF (1 4ml, 6 1) a 0°C se agregó ácido glicolico (90mg, 1 2mmol), HOBt H_2O (0 16g, 1 2mmol) y DIPEA (1 4ml, 8 0mmol) Se agregó EDAC (0 23g, 1 2mmol) a 0°C, luego la mezcla se agitó a temperatura ambiente por 43 horas La solucion se diluyo con DCM (40 ml), a continuacion se lavo con agua (3 x 50ml), solucion molar 1 0 de KOH (50ml), salmuera (50ml) y agua (50ml) El extracto organico se seco y se concentró El residuo se purifico por cromatografía en gel de silice con

MeOH DCM (2 5 97 5) para producir el compuesto del titulo como un solido amarillo palido (0 13g, 28%) NMR 1 19 (t, 1H), 1 48 (d, 6H), 2 58 (s, 3H), 3 01 (m, 4H), 3 44 (m, 2H), 3 83 (m, 2H), 4 21 (s, 2H), 5 57 (septete, 1H), 6 90 (d, 1H), 6 95 (d, 1H), 7 37 (m, 3H), 7 74 (s, 1H), 8 34 (d, 1H), m/z 470

Ejemplo 133

2-(3-Cloro-4-piperazin-1-il)anilino-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina clorhidrato

El compuesto del titulo se preparo de 2-[3-cloro-4-(4-acetilpiperazin-1-il)anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina (Ejemplo 117, 4 1g, 9 1mmol) por el metodo de Ejemplo 131, y se aislo como un solido marrón (1 5g, 94%) NMR 1 40 (d, 6H), 3 09 (m, 4H), 3 15 (s, 3H), 3 18 (m, 4H), 3 29 (m, 1H), 5 37 (septete, 1H), 7 14 (d, 1H), 7 36 (d, 1H), 7 54 (dd, 1H), 7 78 (d, 1H), 8 54 (d, 1H), 9 58 (s, 1H), m/z 430

Ejemplo 134

2-[3-Cloro-4-(4-hidroxiacetilpiperazin-1-il)anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina

El compuesto del titulo se preparo de 2-(3-cloro-4-piperazin-1-il) anilino-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina clorhidrato (Ejemplo 133, 0 40g, 0 86mmol) por el metodo de Ejemplo 132, y se purifico por cromatografía en gel de silice con MeOH DCM (5 95) para producir un solido amarillo (0 25g, 60%) NMR 1 47 (d, 6H), 2 61 (s, 3H), 3 01 (m, 4H), 3 44 (m, 2H), 3 84 (m, 2H), 4 22 (s, 2H), 5 55 (septete, 1H), 6 96 (d, 1H), 7 22 (s, 1H), 7 36 (dd, 1H), 7 57 (d, 1H), 7 65 (d, 1H), 8 26 (d, 1H), m/z 488

Ejemplo 135

2-(3-Cloro-4-{4-[(2*S*)-1-oxopropan-2-ol]piperazin-1-il}anilino)-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina

El compuesto del titulo se preparo de 2-(3-cloro-4-piperazin-1-il) anilino-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina clorhidrato (Ejemplo 133, 0 40g, 0 86mmol) por el metodo de Ejemplo 38 La mezcla de reacción se evaporó bajo presión reducida. El residuo se diluyo con agua (60ml) y se extrajo con DCM (3 x 50ml) Las fases organicas combinadas se lavaron con agua (100ml), luego se secaron y se concentraron El residuo se purifico por cromatografía en gel de silice con MeOH DCM (5 95) para producir el compuesto del titulo como un solido amarillo (0 35g, 88%) NMR 1 39 (d, 3H), 1 46 (d, 6H), 2 60 (s, 3H), 2 80 (s, 1H), 3 01 (m, 4H), 3 60 (m, 2H), 3 77 (m, 1H), 3 79 (m, 1H), 4 52 (q, 1H), 5 51 (septete, 1H), 6 96 (d, 1H), 7 37 (dd, 1H), 7 58 (d, 1H), 7 59 (s, 1H), 7 68 (d, 1H), 8 27 (d, 1H), m/z 502

Ejemplo 136

2-[3-Cloro-4-(4-metoxiacetil)piperazin-1-il]anilino-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina

El compuesto del titulo se preparo de 2-(3-cloro-4-piperazin-1-il) anilino-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina clorhidrato (Ejemplo 133, 0 40g, 0 86mmol) por el método de Ejemplo 38 La mezcla de reacción se evaporó bajo presion reducida El residuo se diluyo con agua (100ml) y se extrajo con cloroformo (3 x 100ml) Las fases organicas combinadas se concentraron bajo presion reducida, luego se diluyeron con EtOAc (100ml) y se lavo con agua (150ml), a continuacion se secaron y se concentraron El residuo se trituro con éter y el solido se purifico por cromatografía en gel de silice con MeOH DCM (5 95) para producir el compuesto del titulo como un sólido amarillo (0 27g, 62%) NMR 1 40 (d, 6H), 2 70 (s, 3H), 2 81 (m, 4H), 3 22 (s, 3H), 3 46 (m, 4H), 4 03 (s, 2H), 5 17 (septete, 1H), 7 03 (d, 1H), 7 24 (dd, 1H), 7 72 (d, 1H), 7 95 (s, 1H), 8 69 (s, 1H), 9 78 (s, 1H), m/z 502

240 238

Ejemplo 137

1-(4-{[5-fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-il] amino}fenil)azetidin-3-ol

(2*Z*)-3-(Dimetilamino)-2-fluoro-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona (Metodo 14, 1 54g, 6 46mM) y sal bicarbonato de *N*-[4-(3-hidroxiazetidin-1-il)fenil]guanidina (Metodo 39, 2 3g, 9 7mM) se agitaron y se calentaron en 2-metoxietanol (17ml) bajo nitrogeno a 130°C por 24 horas El disolvente se retiro *in vacuo* y el residuo se repartio en porciones entre DCM y agua La capa organica se lavo con agua, bicarbonato de sodio diluido, agua, cloruro de sodio saturado y luego se secó con sulfato de sodio anhidro, se filtro y se evaporó El producto crudo se purifico por cromatografía de silice eluyendo con MeOH DCM (5 95) El producto de la columna se trituro con eter, se filtro y se lavo con el mismo disolvente y se secó para producir el compuesto del titulo como un solido marrón (886mg, 18 3%) NMR 1 35 (d, 6H), 2 5 (s, 3H + pico H_2O) 3 4 (t, 2H), 4 0 (t, 2H), 4 5 (q, 1H), 5 42 (m, 1H), 5 53 (d, 1H), 6 37 (d, 2H), 7 28 (m, 3H), 8 4 (d, 1H), 9 07 (s, 1H), m/z 383

Ejemplo 138

1-(4-{[5-Fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-il] amino}fenil)azetidin-3-il-metanosulfonato

A una solución helada de 1-(4-{[5-fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-il]amino}fenil)azetidin-3-ol (Ejemplo 137, 0 728g, 1 905mM) y trietilamina (153µl, 2 09mM) en DCM seco (22ml), se agrego cloruro de mesilo (162µl, 2 09mM) La reacción se agito a 0°C por 30 minutos y a temperatura de la sala por 20 horas La mezcla de reaccion se diluyo con mas DCM y se extrajo a su vez con agua (dos veces), cloruro de sodio saturado, se seco con sulfato de sodio anhidro, se filtro y se evaporo para producir el compuesto del título como una espuma marron (717mg, 82%) NMR 1 37 (d, 6H), 2 48 (s, 3H +DMSO), 3 25 (s, 3H), 3 82 (m, 2H), 4 2 (m, 2H), 5 4 (m, 2H), 6 45 (d, 2H), 7 35 (m, 3H), 8 42 (d, 1H), 9 13 (s, 1H), m/z 461

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Ejemplo 139

N-[4-(3-Azidoazetidin-1-il)fenil]-5-fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-amina

A una solucion de 1-(4-{[5-fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-il]amino}fenil)azetidin-3-il metanosulfonato (Ejemplo 138, 876mg, 1 90mM) en DMF seco (7 3ml), se agrego azida de sodio (619mg, 9 5mM) La reaccion se agito y se calento a 80°C bajo nitrogeno por 18 horas La mezcla de reaccion se diluyo con EtOAc y la solucion se extrajo con agua (dos veces), cloruro de sodio saturado y, a continuacion, se seco con sulfato de sodio anhidro, se filtro y se evaporo El producto crudo se purifico por cromatografía de silice eluyendo con MeOH DCM (2 98) para producir el compuesto del titulo como una espuma marron (389mg, 50%) NMR 1 4 (d, 6H), 2 53 (s, 3H + DMSO), 3 65 (m, 2H), 4 1 (m, 2H), 4 44 (m, 1H), 5 4 (m, 1H), 6 44 (d, 2H), 7 33 (m, 3H), 8 35 (d, 1H), m/z 408

Ejemplo 140

N-[4-(3-Aminoazetidin-1-il)fenil]-5-fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-amina

A una solucion de *N*-[4-(3-azidoazetidin-1-il)fenil]-5-fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-amina (Ejemplo 139, 382mg, 938mM) en THF (10ml), se agrego trifenilfosfina (260mg, 0 984 mM) La reaccion se agitó a temperatura de la sala bajo nitrogeno por 24 horas Seguidamente se agrego agua (2 0ml) y la mezcla se agito y se calento a 65°C por 3 horas Se agrego ácido clorhidrico (1M, 1 5ml) y el THF se retiro *in vacuo* A continuacion se agrego mas agua y la solucion se extrajo con EtOAc Se agrego hidróxido de sodio (1M, 1 5ml) a la capa acuosa y la solución se extrajo con EtOAc Las capas organicas se combinaron, se secaron con sulfato de sodio anhidro, se filtraron y se evaporaron para producir el compuesto del titulo como una espuma amarilla (324mg, 91%) NMR (DMSO-d_6 +d_4-acetic acid) 1 38 (d, 6H), 2 5 (s, 3H),

3 73 (m, 2H), 4 05 (m, 3H), 5 43 (m, 1H), 6 45 (d, 2H), 7 33 (s, 1H), 7 4 (d, 2H), 8 4 (d, 1H), m/z 382

Ejemplo 141

N-[1-(4-{[5-Fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-il]amino}fenil)azetidin-3-il]-2-hidroxiacetamida

A una mezcla de *N*-[4-(3-aminoazetidin-1-il)fenil]-5-fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-amina (Ejemplo 140, 107mg, 0 28mM) y ácido glicolico (26mg, 0 337mM) e hidrato de HOBt (46mg, 0 337mM) en DCM seco (4 0ml), se agregaron diisopropilamina (56µl, 0 337mM) y EDAC (65mg, 0 337mM) La reaccion se agito a temperatura de la sala bajo nitrógeno por 72 horas Se retiro el DCM *in vacuo* y el residuo se disolvió en EtOAc y agua Las capas se repartieron en porciones y se separaron La capa organica se lavó a su vez con agua, bicarbonato de sodio diluido (dos veces), agua, cloruro de sodio saturado y luego se secó con sulfato de sodio anhidro, se filtro y se evaporo El residuo se disolvió en MeOH (2 0ml) y se agrego hidroxido de sodio molar 1 0 (0 25ml) La solución se agitó a temperatura de la sala por 1 hora La mezcla de reaccion se diluyo con EtOAc y agua y las capas se repartieron en porciones y se separaron La capa orgánica se lavó con agua, cloruro de sodio saturado, se seco con sulfato de sodio anhidro, se filtró y se evaporo El producto crudo se trituró con eter, se filtró, se lavo con eter y se seco para producir el compuesto del titulo como un solido amarillo (79mg, 64%) NMR 1 38 (s, 6H), 2 5 (s, 3H + DMSO), 3 64 (t, 2H), 3 8 (d, 2H), 4 03 (t, 2H), 4 63 (m, 1H), 5 37 (t, 1H), 5 45 (m, 1H), 6 4 (d, 2H), 7 33 (m, 3H), 8 28 (d, 1H), 8 4 (d, 1H), 9 08 (s, 1H), m/z 440

Ejemplo 142

N-[1-(4-{[5-Fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-il]amino}fenil)azetidin-3-il]acetamida

A una solucion agitada de *N*-[4-(3-aminoazetidin-1-il)fenil]-5-fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-amina (Ejemplo 140,

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110mg, 0 29mM) y trietilamina (44µl, 0 317mM) en DCM seco (4 0ml), se agrego anhidrido acetico (30µl, 0 317mM) La reaccion se agito a temperatura de la sala bajo nitrogeno por 2 5 horas Se agregaron unas cuantas gotas de MeOH y la solucion se agito por 10 minutos La mezcla de reacción se diluyo entonces con mas DCM y la solucion se extrajo a su vez con agua (dos veces) y cloruro de sodio saturado La capa organica se seco entonces con sulfato de sodio anhidro, se filtro y se evaporo El producto crudo se trituro con eter, se filtró y se lavo con eter y se seco para producir el compuesto del titulo como un solido amarillo (99mg, 81%) NMR 1 4 (d, 6H), 1 8 (s, 3H), 2 5 (s, 3H + DMSO), 3 5 (t, 2H), 4 05 (t, 2H), 4 53 (m, 1H), 5 43 (m, 1H), 6 4 (d, 2H), 7 33 (m, 3H), 8 42 (m,2H), 9 08 (s, 1H), m/z 424

Ejemplo 143

N-[1-(4-{[5-Fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-il]amino}fenil)azetidin-3-il]metanosulfonamida

A una solucion agitada de *N*-[4-(3-aminoazetidin-1-il)fenil]-5-fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-amina (Ejemplo 140, 110mg, 0 29mM) y trietilamina (44µl, 0 317mM) en DCM seco (4 0ml), se agregó metanosulfonil cloruro (25µl, 0 317mM) La reaccion se agito a temperatura de la sala bajo nitrogeno por 24 horas La reaccion se filtro y luego el sólido filtrado se lavó con DCM Se retuvo este solido que era el producto puro Se tomo el filtrado y se agregó mas DCM La solucion se lavó a su vez con agua (dos veces), cloruro de sodio saturado y luego se seco con sulfato de sodio anhidro, se filtró y se evaporo El producto asi obtenido se combinó con el primer lote de producto y los dos se trituraron con éter, se filtraron, se lavaron con éter y se secaron para producir el compuesto del titulo como un solido amarillo NMR 1 4 (d, 6H), 2 6 (s, 3H), 2 9 (s, 3H), 3 55 (t, 2H), 4 13 (t, 2H), 4 25 (m, 1H), 5 37 (m, 1H), 6 4 (d, 2H), 7 33 (d, 2H), 7 58 (d, 1H), 7 75 (d, 1H), 8 5 (d, 1H), 9 22 (s, 1H), m/z 460

Ejemplo 144

(3-Cloro-4-morfolin-4-il-fenil)-[4-(3-isopropil-2-metil-3*H*-imidazol-4-il)-pirimidin-2-il]-amina

El compuesto del título se preparó usando el procedimiento descrito en Ejemplo 112, empleando carbonato de *N*-(3-cloro-4-morfolin-4-il-fenil)-guanidina (Metodo 17, 500mg, 1 97mmol), y (2*E*)-3-(dimetilamino)-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona (Metodo 24 de WO 03/076436, 363mg, 1 64mmol) Rendimiento 412mg, 61% como un solido blanco NMR 1 42 (d, 6H), 2 47 (s, 3H), 2 90 (t, 4H), 3 72 (t, 4H), 5 60 (m, 1H), 7 02 (d, 1H), 7 10 (d, 1H), 7 40 (s, 1H), 7 54 (dd, 1H), 7 78 (d, 1H), 8 37 (d, 1H), 9 43 (s, 1H), m/z 413

Ejemplo 145

(3-Cloro-4-morfolin-4-il-fenil)-[5-fluoro-4-(3-isopropil-2-metil-3*H*-imidazol-4-il)pirimidin-2-il]-amina

El compuesto del titulo se preparo usando el procedimiento descrito en Ejemplo 112, empleando carbonato de *N*-(3-cloro-4-morfolin-4-il-fenil)-guanidina (Metodo 17, 500mg, 1 97mmol), y (2*Z*)-3-(dimetilamino)-2-fluoro-1-(1-isopropil-2-metil-1*H*-imidazol-5il)prop-2-en-1-ona (Metodo 14, 392mg, 1 64mmol) Rendimiento 203mg, 30% como un solido blanco, NMR 1 41 (d, 6H), 2 49 (s, 3H), 2 90 (t, 4H), 3 72 (t, 4H), 5 35 (m, 1H), 7 10 (d, 1H), 7 34 (d, 1H), 7 50 (dd, 1H), 7 73 (d, 1H), 8 52 (d, 1H), 9 51 (s, 1H), m/z 431

Ejemplo 146

N-{4-[2*RS*,6*SR*)-2,6-Dimetilmorfolin-4-il]fenil}-5-fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-amina

(2*E*)-3-(Dimetilamino)-1-(1-etil-2-metil-1*H*-imidazol-5-il)-2-fluoroprop-2-en-1-ona (Metodo 15, 327mg, 1 37mmol) y sal bicarbonato de *N*-[4-(cis-2,6-dimetilmorfolino)fenil]guanidina (Metodo 20, 510mg, 1 65mmol) en 2-metoxietanol (8ml) se calentaron por 17 horas a 110°C La mezcla de reaccion se evaporo bajo presion reducida y el residuo se purifico

por cromatografía en gel de sílice con MeOH DCM EtOAc (4 48 48) a (10 45 45) para producir el compuesto del título, despues de triturar con isohexano, como un sólido (274mg 47 2%) NMR ($CDCl_3$) 1 26 (d, 6H), 1 44 (d, 6H), 1 68 (s, 2H), 2 39 (t, 2H), 2 58 (s, 3H), 3 39 (d, 2H), 3 82 (m, 2H), 5 57 (sept, 1H), 6 82 (s, 1H), 6 89 (d, 2H), 7 37 (d, 2H), 7 57 (d, 1H), 8 22 (d, 1H), m/z 425

Ejemplo 147

Ciclopropilamida de acido (R)-1-{4-[4-(3-isopropil-2-metil-3*H*-imidazol-4-il)-pirimidin-2-ilamino]-fenil}-pirrolidin-2-carboxilico

Ciclopropilamida de acido (R)-1-(4-guanidino-fenil)-pirrolidin-2-carboxilico (Metodo 63, 0 29g, 1 0 mmol) y ((2*E*)-3-(dimetilamino)-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona, (Método 24 de WO 03/076436, 0 15g, 0 68 mmol) se agregaron a 2-metoxietanol (4 ml) y se calentaron a 200°C por 2 horas en el microondas El disolvente se retiro *in vacuo* y la goma se cromatografió cuidadosamente eluyendo con DCM, 1% MeOH/DCM, 2% MeOH/DCM y finalmente 3% MeOH/DCM para producir un solido amarillo (110mg, 36%) NMR (299 954 MHz, $CDCl_3$) 8 28 (d, 1H), 7 39 (d, 1H), 7 34 (s, 1H), 6 85- 6 82 (m, 2H), 6 60-6 57 (m, 3H), 5 61 (septete, 1H), 3 96-3 92 (m, 1H), 3 62 (t, 1H), 3 19 (q, 1H), 2 76-2 67 (m, 1H), 2 56 (s, 3H), 2 30-2 22 (m, 2H), 2 07-1 84 (m, 2H), 1 47 (d, 6H), 0 78-0 70 (m, 2H), 0 45-0 38 (m, 2H), m/z 446

Ejemplo 148

N-(3-Fluoro-4-morfolin-4-fenil)-4-(1-isopropil-2-metil-1*H*-imidazol-5-il) pirimidin-2-amina

(2*E*)-3-(Dimetilamino)-1-(1-isopropil-2-metil-1*H*-imidazol-5-il) prop-2-en-1-ona (Metodo 24 de WO 03/076436), (330mg, 1 5mmol) y sal bicarbonato de *N*-(3-fluoro-4-morfolinofenil)guanidina (Metodo 23, 540mg, 1 8mmol) en 2-metoxietanol (10ml) se calentaron por 49 horas a 100°C La mezcla de reaccion se evaporó bajo presion reducida y el residuo se purifico por cromatografía en gel de sílice con MeOH DCM (2 98 a 6 94) para

producir el compuesto del titulo, luego de trituracion con eter, como un solido (296mg 50%) NMR ($CDCl_3$) 1 51 (d, 6H), 2 59 (s, 3H), 3 06 (t, 4H), 3 89 (t, 4H), 5 68 (septete, 1H), 6 91 (m, 2H), 7 08 (m, 2H), 7 38 (s, 1H), 7 57 (dd, 1H), 8 32 (d, 1H), m/z 397

Ejemplo 149

5-Fluoro-*N*-(3-fluoro-4-morfolin-4-ilfenil)-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-amina

(2*E*)-3-(Dimetilamino)-2-fluoro-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona (Metodo 14, 360mg, 1 5mmol) y sal bicarbonato de *N*-(3-fluoro-4-morfolinofenil)guanidina (Método 23, 540mg, 1 8mmol) en 2-metoxietanol (10ml) se calentaron por 45 horas a 100°C La mezcla de reacción se evaporo bajo presion reducida y el residuo se purifico por cromatografía en gel de sílice con MeOH DCM (3 97) para producir el compuesto del titulo, luego de trituracion con eter, como un solido (298mg 48%) NMR ($CDCl_3$) 1 50 (d, 6H), 2 60 (s, 3H), 3 05 (t, 4H), 3 88 (t, 4H), 5 58 (sept, 1H), 6 90 (m, 2H), 6 95 (d, 1H), 7 08 (dd, 1H), 7 49 (dd, 1H), 7 59 (d, 1H), 8 26 (d, 1H), m/z 415

Ejemplo 150

Ciclopropilamida de acido (*R*)-1-{4-[5-fluoro-4-(3-isopropil-2-metil-3*H*-imidazol-4-il)-pirimidin-2-ilamino]-fenil}-pirrolidin-2-carboxilico

Ciclopropilamida de acido (R)-1-(4-guanidino-fenil)-pirrolidin-2-carboxilico (Metodo 63) (0 36g, 1 25mmol) y (2*Z*)-3-(dimetilamino)-2-fluoro-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona (Metodo 14, 0 15g, 0 63mmol) se agregaron a 2-metoxietanol (4 ml) se calentaron a 200°C por 2 horas en el microondas El disolvente se retiro *in vacuo* y la goma se cromatografio cuidadosamente eluyendo con DCM, 1% MeOH/DCM, 2% MeOH/DCM y finalmente 3% MeOH/DCM para producir un sólido amarillo (180 mg, 62%) NMR (400 132 MHz, $CDCl_3$) 8 21 (d, 1H), 7 56 (d, 1H), 7 34 (d, 2H), 6 80 (s, 1H), 6 59 (m, 3H), 5 55 (septete, 1H), 3 62 (t, 1H), 3 21-3 15 (m, 1H), 2 74-2 68 (m, 1H), 2 58 (s,

3H), 2 28-2 22 (m, 2H), 2 05-1 98 (m, 1H), 1 96-1 86 (m, 1H), 1 45 (d, 6H), 0 79- 0 72 (m, 2H), 0 44-0 37 (m, 2H), m/z 464

Ejemplo 151

N-[(3R)-1-(4-{[5-Fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il) pirimidin-2-il]amino}fenil)pirrolidin-3-il]acetamida

Carbonato de 4-((3*R*)-acetamidopirrolidin-1-il)fenilguanidina (Método 45, 1 25g, 4 28 mmol) y (2*Z*)-3-(dimetilamino)-2-fluoro-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona (Metodo 14, 0 79g, 3 3 mmol) en 2-metoxietanol (20ml) se calentaron a 115°C por 18 horas bajo nitrogeno Luego de la evaporación bajo presion reducida, la cromatografía en gel de silice con MeOH/DCM (100 a 2 5 97 5) produjo el compuesto del titulo, luego de la trituracion con éter, como un sólido color cafe claro (612mg, 43%) NMR 1 38 (d, 6H), 1 80 (s, 3H), 1 80-1 92 (m, 1H), 2 12-2 26 (m, 1H), 2 49 (s, 3H), 2 97-3 03 (m, 1H), 3 14-3 25 (m, 1H), 3 29-3 49 (m, 2H), 4 3-4 41 (m, 1H), 5 20-5 32 (m, 1H), 6 50 (d, 2H), 7 30 (s, 1H), 7 32 (d, 2H), 8 09 (d, 1H), 8 39 (s, 1H), 9 05 (s, 1H), m/z 438

Ejemplo 152

N-[(3S)-1-(4-{[5-Fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il) pirimidin-2-il]amino}fenil)pirrolidin-3-il]acetamida

El compuesto del titulo se preparó por un procedimiento idéntico a Ejemplo 151 más arriba, pero usando carbonato de 4-((3*S*)-acetamidopirrolidin-1-il)fenil guanidina (Metodo 51) NMR 1 37 (d, 6H), 1 81 (s, 3H), 1 78-1 92 (m, 1H), 2 11-2 22 (m, 1H), 2 44 (s, 3H), 2 94-3 06 (m, 1H), 3 14-3 49 (m, 3H), 4 29-4 41 (m, 1H), 5 40-5 43 (m, 1H), 6 49 (d, 2H), 7 30 (s, 1H), 7 32 (d, 2H), 8 09 (d, 1H), 8 40 (d, 1H), 9 03 (s, 1H), m/z 438

Ejemplo 153

N-{4-[(3S)-3-Aminopirrolidin-1-il]fenil}-5-fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-amina

N-[(3*S*)-1-(4-{[5-Fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il) pirimidin-2il]amino}fenil)pirrolidin-3-il]acetamida (Ejemplo 152, 0 49g, 1 12 mmol) en isopropanol (20ml), agua (5ml) y ácido clorhídrico (2 ml) se calento a reflujo bajo nitrógeno por 18 horas Luego de la evaporacion bajo presion reducida, la mezcla se disolvió en agua (15ml) y se ajusto a pH 9 con solución de hidróxido de amonio acuoso La solucion se extrajo con DCM (3 x 15 ml), se secó y luego de la evaporacion bajo presion reducida para producir el compuesto del título como un sólido (0 42g, 95%) NMR 1 38 (d, 6H), 1 61-1 73 (m, 1H), 2 00-2 13 (m, 1H), 2 44 (s, 3H), 2 80-2 88 (m, 1H), 3 12-3 20 (m, 1H), 3 20-3 42 (m, 2H), 3 49-3 60 (m, 1H), 5 40-5 51 (m, 1H), 6 46 (d, 2H), 7 30 (d, 2H), 7 33 (s, 1H), 8 40 (s, 1H), 9 00 (s, 1H), m/z 396

Ejemplo 154

(2*S*)-*N*-[(3*S*)-1-(4-{[5-Fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il) pirimidin-2-il]amino}fenil)pirrolidin-3-il]-2-hidroxipropanamida

N-{4-[(3*S*)-3-Aminopirrolidin-1-il]fenil)-5-fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-amina (Ejemplo 153, 220mg, 0 556mmol), ácido L-láctico (61mg, 0 667mmol), monohidrato de HOBt (103mg, 0 667 mmol) y base de Hünig (0 12ml, 0 667mmol) en DCM (5ml) se hicieron reaccionar con EDAC (128mg, 0 667mmol) a temperatura de la sala bajo nitrógeno por 18 horas La mezcla se diluyó con DCM (20ml) y se lavó con agua (20ml), 1N de hidróxido de potasio acuoso (20ml) y cloruro de sodio acuoso saturado (15ml) La mezcla se seco y luego de la evaporación bajo presion reducida se purificó por HPLC en una columna Fenomenex, (0-50% acetonitrilo/agua, 0 2% TFA) Las fracciones se diluyo con agua (20ml), se basificó con carbonato de potasio sólido, y se extrajo dos veces con EtOAc/DCM (2oml, 2 1) La solución se lavo con cloruro de sodio acuoso saturado (15ml), se seco y, luego de la evaporacion bajo presión reducida, produjo el compuesto del titulo como un sólido amarillo, (79mg, 30%) ,NMR 1 20 (d, 3H), 1 37 (d, 6H), 1 90-2 04 (m, 1H), 2 11-2 27 (m, 1H), 2 47 (s, 3H), 3 00-3 09 (m, 1H), 3 20-3 47 (m, 3H),

3 91-4 00 (m, 1H), 4 32-4 47 (m, 1H), 5 38 (s, 1H), 5 40-5 49 (m, 1H), 6 49 (d, 2H), 7 30 (s, 1H), 7 32 (d, 2H), 7 76 (d, 1H), 8 40 (d, 1H), 9 06 (s, 1H), m/z 468

Ejemplo 155

N-[(3*S*)-1-(4-{[5-Fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il) pirimidin-2-il]amino}fenil)pirrolidin-3-il]-2-hidroxiacetamida

El compuesto del titulo se preparo (38mg, 15%) usando un procedimiento análogo a Ejemplo 154, a partir de *N*-{4-[(3*S*)-3-aminopirrolidin-1-il]fenil}-5-fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-amina (Ejemplo 153, 220mg, 0 556 mmol) y acido glicolico (51mg, 0 667 mmol) NMR 1 39 (d, 6H), 1 91-2 04 (m, 1H), 2 13-2 25 (m, 1H), 2 44 (s, 3H), 3 04-3 12 (m, 1H), 3 18-3 47 (m, 3H), 3 80 (d, 2H), 4 38-4 47 (m, 1H), 5 32 (t, 1H), 5 40-5 52 (m, 1H), 6 50 (d, 2H), 7 30 (s, 1H), 7 35 (d, 2H), 7 82 (d, 1H), 8 40 (d, 1H), 9 04 (s, 1H), m/z 454

Ejemplo 156

N-{4-[(3*R*)-3-Aminopirrolidin-1-il]fenil}-5-fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-amina

El compuesto del titulo se preparó de manera identica, (0 45g, 99%), a Ejemplo 153 a partir de *N*-[(3R)-1-(4-{[5-fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-il]amino}fenil)pirrolidin-3-il]acetamida (Ejemplo 151) NMR 1 36 (d, 6H), 1 61-1 76 (m, 1H), 2 00-2 16 (m, 1H), 2 47 (s, 3H), 2 79-2 89 (m, 1H), 3 14-3 41 (m, 3H), 3 28 (brs, 2H), 3 50-3 60 (m, 1H), 5 40-5 52 (m, 1H), 6 44 (d, 2H), 7 31 (d, 2H), 7 35 (s, 1H), 8 39 (d, 1H), 9 00 (s, 1H), m/z 396

Ejemplo 157

(2*S*)-*N*-[(3*R*)-1-(4-{[5-Fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il) pirimidin-2-il]amino}fenil)pirrolidin-3-il]-2-hidroxipropanamida

El compuesto del titulo se preparo (15mg, 6%) usando un procedimiento análogo a Ejemplo 154 a partir de *N*-{4-[(3*R*)-3-

aminopirrolidin-1-il]fenil}-5-fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-amina (Ejemplo 156, 220mg, 0 556 mmol) y ácido L-lactico (61mg, 0 667 mmol) NMR 1 20 (d, 3H), 1 36 (d, 6H), 1 89- 2 01 (m, 1H), 2 14-2 22 (m, 1H), 2 43 (s, 3H), 3 02-3 10 (m, 1H), 3 14-3 48 (m, 3H), 3 92-4 03 (m, 1H), 4 34-4 46 (m, 1H), 5 35 (d, 2H), 5 41-5 53 (m, 1H), 6 49 (d, 2H), 7 30 (s, 1H), 7 32 (d, 2H), 8 40 (d, 1H), 9 05 (s, 1H), m/z 468

Ejemplo 158

N-[(3*R*)-1-(4-{[5-Fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il) pirimidin-2-il]fenil)pirrolidin-3-il]-2-hidroxiacetamida

El compuesto del título (38mg, 15%) se preparo usando un procedimiento análogo a Ejemplo 155 a partir de *N*-{4-[(3*R*)-3-aminopirrolidin-1-il]fenil}-5-fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-amina (Ejemplo 156, 220mg, 0 556 mmol) y ácido glicólico (51mg, 0 667 mmol) NMR 1 39 (d, 6H), 1 92-2 04 (m, 1H), 2 14-2 26 (m, 1H), 2 44 (s, 3H), 3 04-3 13 (m, 1H), 3 18-3 49 (m, 3H), 3 80 (d, 2H), 4 46-4 51 (m, 1H), 5 34 (t, 1H), 5 42-5 51 (m, 1H), 6 49 (d, 2H), 7 31 (d, 1H), 7 35 (d, 2H), 7 82 (d, 1H), 8 41 (d, 1H), 9 06 (s, 1H), m/z 454

Ejemplo 159

Dimetilamida de acido (S)-1-{4-[5-fluoro-4-(3-isopropil-2-metil-3*H*-imidazol-4-il)-pirimidin-2-ilamino]-fenil}-pirrolidine-2-carboxilico

Dimetilamida de ácido (S)-1-(4-guanidino-fenil)-pirrolidin-2-carboxilico (Método 54, 0 5g, 1 82mmol) y (2*Z*)-3-(dimetilamino)-2-fluoro-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona (Metodo 14, 0 2g, 0 83mmol) se calentaron a reflujo en butanol (7 ml) de un dia para otro LCMS indico tan solo 7% del producto La reaccion se paso a un tubo microondas y se calentó a 200°C por 2 horas LCMS indicó 15% de material de partida y principalmente producto El disolvente se retiro *in vacuo* y se cromatografió El producto se purificó por HPLC y las fracciones requeridas se combinaron y se basificaron con K_2CO_3 (0 5 g), se extrajeron con DCM (2 x 50 ml), se secaron, y el disolvente se retiro *in*

vacuo para producir un sólido amarillo (101mg, 31%) NMR (400 132 MHz, $CDCl_3$) 8 18 (d, 1H), 7 56 (d, 1H), 7 24 (d, 2H), 6 69 (s, 1H), 6 42 (d, 2H), 5 59 (septete, 1H), 4 51 (dd, 1H), 3 64 (dt, 1H), 3 41 (q, 1H), 3 16 (s, 3H), 2 98 (s, 3H), 2 56 (s, 3H), 2 38-2 28 (m, 1H), 2 25-2 14 (m, 1H), 2 08-1 98 (m, 2H), 1 39 (t, 6H), m/z 452

Ejemplo 160

Metilamida de acido (*R*)-1-{4-[5-fluoro-4-(3-isopropil-2-metil-3*H*-imidazol-4-il)-pirimidin-2-ilamino]-fenil}-pirrolidin-2-carboxilico

Metilamida de acido (*R*)-1-(4-guanidino-fenil)-pirrolidin-2-carboxilico (Metodo 59, 0 22g, 0 82mmol) y (2*Z*)-3-(dimetilamino)-2-fluoro-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona (Metodo 14, 0 15g, 0 63mmol) se agregaron a 2-metoxietanol (4 ml) y se calentaron a 200°C por 2 horas en el microondas Se retiro el disolvente *in vacuo* y se cromatografio El producto se purifico por HPLC, y las fracciones requeridas se combinaron y se basificaron con K_2CO_3 (0 5 g), se extrajeron con DCM (2 x 50 ml), se secaron, y el disolvente se retiró *in vacuo* para producir un sólido amarillo (110mg, 40%) NMR (400 132 MHz, $CDCl_3$) 8 21 (d, 1H), 7 56 (d, 1H), 7 34 (d, 2H), 6 79 (s, 1H), 6 60 (d, 2H), 6 56 (s, 1H), 5 56 (septete, 1H), 3 99 (t, 1H), 3 64 (t, 1H), 3 20 (q, 1H), 2 80 (d, 3H), 2 58 (s, 3H), 2 29-2 24 (m, 2H), 2 06-1 89 (m, 2H), 1 45 (d, 6H), m/z 438

Ejemplo 161

Metilamida de acido (*R*)-1-{4-[4-(3-isopropil-2-metil-3*H*-imidazol-4-il)-pirimidin-2-ilamino]-fenil}-pirrolidin-2-carboxilico

Metilamida de acido (*R*)-1-(4-guanidino-fenil)-pirrolidin-2-carboxilico (Metodo 59, 0 27g, 1 0 mmol) y (2*E*)-3-(dimetilamino)-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona, (Metodo 24 de WO 03/076436, 0 15g, 0 0 68 mmol) se agregaron a 2- metoxietanol (4 ml) y se calentaron a 200°C por 2 horas en el microondas El disolvente se retiro *in vacuo* y la goma se cromatografio cuidadosamente eluyendo con DCM,

1%MeOH/DCM, 2% MeOH/DCM y finalmente 3%MeOH/DCM para producir un solido amarillo (101mg, 35%) NMR (400 132 MHz, $CDCl_3$) 8 28 (d, 1H), 7 39 (d, 2H), 7 34 (s, 1H), 6 89 (s, 1H), 6 83 (d, 1H), 6 61-6 57 (m, 3H), 5 62 (septete, 1H), 3 99 (t, 1H), 3 65 (t, 1H), 3 24-3 17 (m, 1H), 2 80 (d, 3H), 2 55 (s, 3H), 2 29-2 24 (m, 2H), 2 06-1 89 (m, 2H), 1 46 (d, 6H), m/z 420

Ejemplo 162

N-[(3*R*)-1-(4-{[4-(1-Isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-il] amino}fenil)pirrolidin-3-il]acetamida

Sal de trifluoroacetato de 4-((3*R*)-acetamidopirrolidin-1-il)fenil guanidina (Método 70, 1 79g, 4 55mmol), (2*E*)-3-(dimetilamino)-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona (Metodo 24 de WO 03/076436, 1 01g, 4 55mmol) en 2-metoxietanol (20ml) y DIPEA (1 74ml, 10mmol) se calentaron a 115°C por 20 horas bajo nitrogeno Luego de la evaporación bajo presión reducida, cromatografía en gel de silice con MeOH/DCM (100 a 5 95) produjo el compuesto del titulo, luego de la trituracion con eter, como un sólido amarillo (165mg, 9%) NMR 1 39 (d, 6H), 1 75-1 90 (m, 1H), 1 80 (s, 3H), 2 11-2 22 (m, 1H), 2 44 (s, 3H), 2 98-3 02 (m, 1H), 3 16-3 48 (m, 3H), 4 28-4 37 (m, 1H), 5 64-5 75 (m, 1H), 6 50 (d, 2H), 6 89 (d, 1H), 7 35 (s, 1H), 7 37 (d, 1H), 8 09 (d, H), 8 98 (s, H) m/z 420

Ejemplo 163

N-[(3R)-1-(2-Fluoro-4-{[4-(1-isopropil-2-metil-1*H*-imidazol-5-il) pirimidin-2-il]amino-2-fluoro}fenil)pirrolidin-3-il]acetamida

El compuesto del titulo (0 24g, 10%), se preparó por una ruta analoga a Ejemplo 162, a partir de carbonato de 2-fluoro-4-((3R)-acetamidopirrolidin-1-il)fenil guanidina (Metodo 69, 1 16g, 5 23 mmol) y (2*E*)-3-(dimetilamino)-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona, (Metodo 24 de WO 03/076436, 2 43g, 7 84 mmol) NMR 2 41 (d, 6H), 1 70-1 86 (m, 1H), 1 80 (s, 3H), 2 07-2 18 (m, 1H), 2 46 (s, 3H), 3 04-

3 12 (m, 1H), 3 19-3 28 (m, 1H), 3 32-3 49 (m, 2H), 4 22-4 39 (m, 1H), 5 62-5 72 (m, 1H), 6 68 (t, 1H), 6 98 (d, 2H), 7 21 (d, 1H), 7 39 (s, 1H), 7 50 (d, 1H), 8 07 (d, 1H), 8 32 (d, 1H), 9 24 (s, 1H), m/z 438

Preparación de Materiales de Partida

Método 1

N-{4-[4-(Metilsulfonil)piperazin-1-il]fenil}guanidina

1-Metilsulfonil-4-(4-nitrofenil)piperazina [J Med Chem 20 (8) 987-996 (1977)] (24g) en EtOH (250 ml) se hidrogenó sobre 10% Pd/carbono (2 4 g) a temperatura y presión ambiente La reaccion se filtró y el catalizador y el sólido insoluble se lavaron con MeOH 2N ácido clorhídrico (100 100 ml) La evaporacion bajo presión reducida produjo el clorhidrato de anilina como un sólido anaranjado (19 8 g 81%) M/z 256

Una mezcla de la anilina (4 7g 16 1 mmol) y la cianamida (800 mg 19 0 mmol) en EtOH (25 ml) y 1,4-dioxano (25 ml) se calentaron a 90°C - 95°C por un total de 19 horas Se agregaron más cianamida (450 mg) y EtOH (10 ml) luego de 5 5 horas La mezcla de reacción se evaporó bajo presión reducida. Se agrego agua (100 ml) al residuo antes de basificar con 40% de hidroxido de sodio (pH > 11) El sólido se extrajo por filtracion, se lavó con un poco de agua fria, se secó sobre un filtro, luego se paso a un vaso de pico El residuo se trituró con acetona (50 ml), se filtro y se seco con aire para producir el compuesto del título (3 2 g 58%) NMR 2 89 (s, 3H), 3 08 (m, 4H), 3 21 (m, 4H), 3 30 (b s, 4H), 6 73 (d, 2H), 6 73 (d, 2H), m/z 298

Método 2

Sal bicarbonato de *N*-[4-(4-acetilpiperazin-1-il)fenil]guanidina

1-Acetil-4-(4-nitrofenil)piperazina [J Med Chem 20(8) 987-996 (1977)] (20 8 g) en EtOH (200 ml) se hidrogenó sobre 10% Pd/carbono (2 1 g) a temperatura y presión ambiente El catalizador se extrajo por filtracion,

se lavo con EtOH (500 ml) y la evaporacion bajo presión reducida para producir la anilina como un solido púrpura, 22g (aun humedo)

La anilina (5 0 g 22 8 mmol) se agitó en 1,4-dioxano seco (55 ml) y EtOH (20 ml) Luego se agrego 4N HCl en dioxano (6 0 ml 25 mmol), despues de 3 a 4 minutos se agregaron cianamida (1 6 g 38 1 mmol) y mas EtOH (4 ml) La reaccion se calento a 95°C por 17 5 horas, luego se agregaron más cianamida (300 mg) y 4N HCl/dioxano (2 ml) La reaccion se continuo calentando por 6 horas Luego de la evaporacion bajo presion reducida, el solido se trituro con eter (2x70 ml) y se seco con aire El solido se disolvio en agua (40 ml), lentamente se agrego solución de bicarbonato de sodio saturado (75 ml) agitando al mismo tiempo Luego de 21 horas, se recogio el solido mediante filtración, se lavó con acetona (2x40 ml) y se seco bajo vacio (5 7g 77%) NMR 2 01 (s, 3H), 2 98 (t, 2H), 3 05 (t, 2H), 2 9-3 8 (v b s, intercambiables), 3 54 (m, 4H), 6 81 (d, 2H), 6 88 (d, 2H), m/z 262

Método 3

(2*E*)-2-Cloro-3-(dimetilamino)-1-(1-isopropil-2-metil-1*H*-imidazol-5- prop-2-en-1-ona

Dicloroyodato de benciltrimetilamonio (2 6g 7 5mmol) se agrego en porciones a una solucion agitada de (2*E*)-3-(dimetilamino)-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona (Método 24 de WO 03/076436, 1 1g 5mmol) en MeOH/DCM (15/30ml) a temperatura de la sala Luego de 1 hora se agregaron agua (10ml) y DCM (20ml) seguidos, despues de 30 minutos mas, por solución de bicarbonato de sodio saturado (20ml) Los organicos se separaron, se re-extrajeron los acuosos con DCM (25ml) Los orgánicos combinados se lavaron con 5% (p/v) de solucion de tiosulfato de sodio (30 a 35ml) y salmuera (25ml), se secaron (Na_2SO_4) y se evaporaron para producir el compuesto del titulo como un aceite (rendimiento crudo 1 68 g aun humedo) M/z 256

Metodo 4

Sal bicarbonato de *N*-[4-(morfolino)fenil]guanidina

4-Morfolinoanilina (1 78g 10mmol) y cianamida (420mg 10mmol) se agitaron en 1,4-dioxano (17 5ml) 7N HCl en 1,4-dioxano (2 5ml) se agrego lentamente antes de calentar a 95°C por 11 horas La mezcla de reaccion se evaporó bajo presion reducida y el solido se trituro con eter antes de secar con aire de un dia para otro Este solido se trato con agua (20ml) y se agitó durante la lenta adicion de solucion de bicarbonato de sodio acuoso saturado (15ml) El solido se recogio por filtracion, se lavo con acetona (15ml) y se secó con aire para producir el compuesto del titulo 2 3g 80% NMR 2 95 (4H, m), 3 39 (intercambiables, v brs), 3 68 (4H, m), 6 68 (2H, d), 6 71 (2H, d), m/z 221

Método 5

2-Amino-5-cloro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina

Una solucion de 2-amino-4-(1-isopropil-2-metil-1*H*-imidazol-5-il) pirimidina (Metodo 39 de WO 03/076436, 0 5g, 2 3mmol) y N-clorosuccinimida (0 4g, 3mmol) en acido acetico (5 ml) se agitó a 65°C bajo nitrógeno por 2 horas A continuacion, la mezcla de reaccion se dejo enfriar a temperatura de la sala y el disolvente se retiro bajo vacio El crudo se absorbio en EtOAc y agua, luego se agregaron porciones de carbonato de potasio solido a esta solucion bifásica agitada hasta que se alcanzo un pH 8-9 Las dos capas se separaron, la capa acuosa se extrajo una vez con EtOAc, luego los organicos se combinaron, se lavaron con salmuera y se secaron El retiro del disolvente dejó un residuo, el cual se purificó en silice (MeOH/DCM/EtOAc, de 0/50/50 a 6/47/47) Triturar la espuma en eter produjo un solido blanco, el cual se extrajo por filtracion (0 49g, 85%) NMR ($CDCl_3$) 1 51 (d, 6H), 2 55 (s, 3H), 4 85 (septuplete, 1H), 5 01 (b s, 2H), 7 48 (s, 1H), 8 31 (s, 1H), m/z 252 (^{35}Cl), 254 (^{37}Cl), m/z 250 (^{35}Cl), 252 (^{37}Cl)

Método 6

4-[*N*-(Propionil)-*N*-(isopropil)amino]-5-metilisoxazol

Trietilamina (1 0 equivalente) se agrego gota a gota durante 45 minutos a una solucion de *N*-isopropil-5-metilisoxazol-4-amina (Método 1 de WO 03/76436, 258g, 1 0 equivalente) y cloruro de *n*-propionilo (1 0 equivalente) en DCM (8 6 vol equivalentes) a -3°C La reaccion se agito entonces a 0°C por 20 minutos y, luego, se dejo calentar a temperatura de la sala de un día para otro Se agregó agua (10 vol equivalentes) y la mezcla se agito entonces por 30 minutos La capa orgánica se separo y se lavo con agua (2 x10 vol equivalentes), 2M HCl (3 x10 vol equivalentes), salmuera (10 vol equivalentes), se secó, se filtró y el disolvente se retiro entonces *in vacuo* del filtrado para dejar un aceite amarillo, el cual se cristalizó al reposar (330g, 91%) NMR 0 91 (3H, t), 0 95 (6H, b s), 1 9 (2H, q), 2 35 (3H, s), 4 8(1H, septuplete), 8 61 (1H, s)

Metodo 7

N-[(*E*)-1-Acetil-2-aminoetenil]-*N*-isopropilpropanamida

4-[*N*-(Propionil)-*N*-(isopropil)amino]-5-metilisoxazol (Método 6, 330g, 1 0 equivalente) se agitó bajo hidrógeno (1 0 equivalente), con 10% paladio sobre carbono (0 1 equivalente) en EtOH (10 vol equivalentes) a 25°C de un dia para otro El catalizador se retiro por filtración y el EtOH se retiro *in vacuo* para dejar un solido blancuzco (351g, 98%) Este se utilizó sin purificacion posterior

Método 8

1-Isopropi-2-etil-5-acetilimidazol

N-[(*E*)-1-Acetil-2-aminoetenil]-*N*-isopropilpropanamida (Metodo 7, 373g, 1 0 equivalente) se agito con hidróxido de sodio (1 4 equivalentes) en EtOH (4 vol equivalentes) La reaccion se calento a reflujo (85°C) y se agito de un día para otro A continuación se agregó cloruro de amonio (2 0 equivalentes) y éste se agito por 2 horas (la consistencia de la reaccion cambió a un precipitado fino) En seguida se dejo enfriar la reaccion, el

solido se extrajo por filtracion y se descarto, y el disolvente se retiro entonces *in vacuo* A continuación se agregó agua al residuo, el solido se extrajo por filtracion y se descarto A continuacion se retiro el disolvente *in vacuo* Entonces de realizo cromatografía preparativa eluyendo con 5% MeOH / DCM, para dejar un aceite marron (290g, 86%) NMR 1 23 (3H, t), 1 43 (6H, d), 2 40 (3H, s), 2 77 (2H, q), 5 0 (1H, b s), 7 87 (1H, s)

Metodo 9

5-(3-Dimetilaminoprop-2-en-1-oil)-1-isopropil-2-etilimidazol

1-Isopropi-2-etil-5-acetilimidazol (Metodo 8, 290g, 1 0 equivalente) se agito con DMF DMA (2 0 equivalente) en DMF (15 vol equivalente) La reaccion se calento a 130°C y se agito de un dia para otro La reaccion se dejo enfriar y el disolvente se retiro *in vacuo* El residuo se trituro con eter y el solido marron se extrajo por filtracion, se lavo con eter, este proceso se repitio A continuación los filtrados se combinaron y se purificaron por cromatografía preparativa eluyendo con 5% MeOH / DCM para producir un solido amarillo (223g, 59%) NMR 1 24 (3H, t), 1 46 (6H, d), 2 73 (2H, q), 2 96 (6H, b s), 5 09 (1H, septuplete), 5 56 (1H, d), 7 51 (1H, s), 7 53 (1H, d)

Método 10

4-(*N*-Butiril-*N*-etilamino)-5-metilisoxazol

A una solucion helada, agitada, de 4-etilamino-5-metilisoxazol (Método 5 de WO 03/76436, 49 6g, 305mM) y trietilamina (77 0g, 763mM, 107ml) en DCM (800ml), se agrego lentamente una solución de cloruro de *n*-butirilo (35 5, 333mM, 35ml) en DCM (100ml) Hubo una exoterma moderada La solución se dejo calentar a temperatura ambiente y agitar por 1 hora La mezcla de reacción se lavo con agua, 2N HCl, salmuera, $NaHCO_3$ saturado y salmuera Se seco y el disolvente se evaporo para producir el compuesto del titulo como un aceite, el cual se cristalizo en un solido ceroso (45 1g, 75%) NMR (300Mz, DMSO-d_6) 0 78 (t, 3H), 0 96

(t, 3H), 1 44 (sext, 2H), 1 93 (t, 2H), 2 33 (s, 3H), 3 49 (q, 2H), 8 68 (s, 1H), m/z 197

Método 11

N-[-1-Acetil-2-aminoetenil)-*N*-etilbutanamida

Una solucion de 4-(*N*-butiril-*N*-etilamino)-5-metilisoxazol (Metodo 10, 45g, 230mM) en EtOH (1 51) se hidrogeno sobre 10% Pd/C (11 25g) a 4 bares El catalizador se extrajo por filtracion y la solucion se evaporó El residuo se trituró con eter y el intermedio cristalino se extrajo por filtracion (33 94g) Este se utilizo sin purificacion posterior

Metodo 12

1-Etil-2-propil-5-acetilimidazol

Una solución de *N*-[(*E*)-1-acetil-2-aminoetenil]-*N*-etilbutanamida (Metodo 11, 33 9g, 171mM) y NaOH (8 2g, 205mM) en EtOH (400ml) se calentó bajo reflujo por 4 horas NH_4Cl (11 9g, 222mM) se agrego a la solucion caliente, la cual se dejo enfriar y agitar por 48 horas La mezcla de reaccion se filtro y la solucion se evaporó El residuo se tomo en eter y se filtro nuevamente La solucion se evaporó para producir el compuesto del titulo como un solido amarillo (30 55g, 74%) NMR (300Mz, DMSO-d6) 0 92 (t, 3H), 1 17 (t, 3H), 1 70 (sext, 2H), 2 37 (s, 3H), 2 64 (t, 2H), 4 23 (q, 2H), 7 83 (s, 1H), m/z 181

Metodo 13

5-(3-Dimetilaminoprop-2-en-1-oil)-1-etil-2-propilimidazol

Una solucion de 1-etil-2-propil-5-acetilimidazol (Metodo 12, 30 5g, 169mM) y DMF DMA (49 7g, 338mM, 58ml) en DMF (100ml) se agito a 130°C por 18 horas, permitiendo la destilacion del EtOH generado Al enfriar, el producto se cristalizó de la mezcla de reacción y se filtro y se lavo con eter (20 94g) Se obtuvo una segunda cosecha al evaporar el disolvente y triturar con eter (8 8g) (29 74g, 75%) NMR (300Mz, DMSO-

d_6) 0 92 (t, 3H), 1 18 (t, 3H), 1 70 (sextete, 2H), 2 60 (t, 2H), 2 94 (brs, 6H), 4 30 (q, 2H), 5 56 (d, 1H), 7 50 (d, 1H), 7 56 (s, 1H), m/z 236

Metodo 14

(2*Z*)-3-(Dimetilamino)-2-fluoro-1-(1-isopropil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona

A una solución agitada de (2*E*)-3-(dimetilamino)-1-(1-isopropil-2-metil-1Himidazol-5-il)prop-2-en-1-ona, (Metodo 24 de WO 03/076436, 5 53g, 25mmol) en MeOH (100ml) a temperatura ambiente, se agrego en porciones durante ~5 minutos selectfluor® (14 16g, 40mmol) Se mantuvo la temperatura a 25-30°C enfriando ligeramente Luego de agitar por 90 minutos, la mezcla de reacción se enfrio en hielo/acetona y se filtro El filtrado se evaporo bajo presión reducida y el residuo se tomo en DCM Se lavo con amoniaco acuoso, salmuera, se seco con Na_2SO_4 anhidro y se evaporo bajo presion reducida. El compuesto del titulo se aisló por MPLC en gel de silice usando dos columnas separadas (10% EtOH/ EtOAc, luego 3 5%EtOH/DCM) como un aceite viscoso dorado, el cual se cristalizo al reposar durante varias semanas Rendimiento = 2 50g (42%) NMR (300Mz) 1 40 (d, 6H), 2 38 (s, 3H), 3 05 (s, 6H), 4 70 (septete, 1H), 6 96 (d, 1H), 7 08 (s, 1H), ^{19}F NMR (376MHz) -166 7 (d), m/z 240

Método 15

(2*Z*)-3-(Dimetilamino)-1-(1-etil-2-metil-1*H*-imidazol-5-il)-2-fluoroprop-2-en-1-ona

El compuesto del titulo se preparo por el procedimiento de Metodo 14 mas arriba en una escala 46mM de (2*E*)-3-(dimetilamino)-1-(1-etil-2-metil-1*H*-imidazol-5-il)prop-2-en-1-ona (Metodo 16 de WO 02/20512) El compuesto del titulo se aislo por MPLC en gel de silice usando dos columnas separadas (5% EtOH/DCM, luego 10% EtOH/EtOAc) y se cristalizo fácilmente en la trituración con éter Rendimiento = 3 93g (38%) NMR (300Mz) 1 2 (t, 3H), 2 38 (s, 3H), 3 05 (s, 6H), 4 18 (q, 2H), 6 96 (d, 1H), 7 34 (s, 1H), ^{19}F NMR (376MHz) -168 2 (d), m/z 226

Método 16

(2*Z*)-1-(1-Ciclobutil-2-metil-1*H*-imidazol-5-il)-3-(dimetilamino)-2-fluoroprop-2-en-1-ona

El compuesto del titulo se preparó de (2*E*)-1-(1-ciclobutil-2-metil-1*H*-imidazol-5-il)-3-(dimetilamino)prop-2-en-1-ona (Metodo 37 de WO 03/076435, 3 0g) por el procedimiento de Metodo 14 La purificacion por cromatografía en gel de silice eluyendo con EtOH/EtOAc (5 95 a 10 90) proporcionó el compuesto del titulo como un sólido amarillo (1 64g, 51%) NMR ($CDCl_3$) 1 73-1 88 (m, 2H), 2 47 (s, 3H), 2 45-2 55 (m, 4H), 3 10 (s, 6H), 5 00 (quintete, 1H), 6 87 (d, 1H), 7 23 (d, 1H), m/z 252

Metodo 17

Sal bicarbonato de *N*-(3-cloro-4-morfolin-4-il-fenil)-guanidina

El compuesto del titulo se preparó usando el procedimiento descrito mas arriba para Metodo 4 usando *N*-(4-amino-2-clorofenil)morfolina (1 1g, 5 19mmol), cianamida (273mg, 6 49mmol), 4 0M HCl en dioxano (1 62ml, 6 49mmol) y dioxano (30ml) Rendimiento 820mg, 50% NMR 2 85 (t, 4H), 3 70 (t, 4H), 6 73 (dd, 1H), 6 81 (d, 1H), 7 00 (d, 1H)

Metodo 18

1-(Cis-2,6-dimetilmorfolino)-4-nitrobenceno

1-Fluoro-4-nitrobenceno (4 9g, 34 75 mmol) se agrego a cis-2,6-dimetilmorfolina (44 4g, 38 26 mmol) y carbonato de potasio anhidro (2 5g, 18 12 mmol) en acetonitrilo (50ml) La reacción se calento bajo reflujo por 19 horas, se enfrio, se filtró y el solido se lavó con acetonitrilo La evaporación del filtrado produjo el compuesto del titulo como un solido amarillo (8 1g, 99%) NMR ($CDCl_3$) 1 28 (d, 6H), 2 61 (t, 2H), 3 66 (td, 2H), 3 76 (m, 2H), 6 82 (d, 2H), 8 13 (d, 2H), m/z 237

Metodo 19

4-(Cis-2,6-dimetilmorfolino)anilina

1-(Cis-2,6-dimetilmorfolino)-4-nitrobenceno (Método 18, 8g) en EtOH (100ml) se redujo con hidrogeno durante 10% paladio/carbono (800mg) a 50°C Luego de extraer por filtracion el catalizador y lavar con EtOH, la evaporacion del filtrado produjo el compuesto del titulo como un aceite marron/rojo, el cual empezo a solidificar despues de varios dias (rendimiento cuantitativo) NMR ($CDCl_3$) 1 23 (d, 6H), 2 33 (t, 2H), 3 25 (d, 2H), 3 81 (m, 2h), 6 65 (d, 2H), 6 79 (d, 2H), m/z 207

Metodo 20

Sal bicarbonato de *N*-[4-(cis-2,6-dimetilmorfolino)fenil]guanidina

4-(Cis-2,6-dimetilmorfolino)anilina (Método 19, 6g, 29 10mmol) y cianamida (1 5g, 35 71mmol) se agitaron en 1,4-dioxano (45ml) 4N HCl en 1,4-dioxano (8 8ml, 35 2mmol) se agrego lentamente antes de calentar a 100°C por 1 75 horas La mezcla de reaccion se evaporo bajo presion reducida y el residuo se trituró con éter La goma resultante se trato con agua (30ml) y se agito durante la lenta adición de solución de bicarbonato de sodio acuoso saturado (40ml) El sólido se recogio por filtracion, se lavó con acetona (2x25ml) y se seco por aire para producir el compuesto del título (6 4g 71 %) NMR 1 15 (d, 6H), 2 21 (t, 2H), 3 48 (td, 2H), 3 68 (m, 2H), 6 85 (d, 2H), 6 89 (brd, 2H), m/z 249

Método 21

1-Fluoro-2-morfolino-5-nitrobenceno

1,2-Difluoro-4-nitrobenceno (8 0g, 50 mmol) se agrego a morfolina (4 85g, 55 7 mmol) y carbonato de potasio anhidro (3 85g, 27 9 mmol) en acetonitrilo (75ml) La reaccion se calentó a 85°C por 3 horas, se enfrio, se filtró y el solido se lavo con EtOAc (50ml) La evaporacion del filtrado, la trituracion con isohexano y la filtracion produjeron el compuesto del titulo como un sólido (11 2g, 98%) NMR ($CDCl_3$) 3 28 (t, 4H), 3 88 (t, 4H), 6 92 (t, 1H), 7 92 (dd, 1H), 8 00 (m, 1H), m/z 227

Método 22

3-Fluoro-4-morfolinoanilina

1-Fluoro-2-morfolino-5-nitrobenceno (Método 21, 9g) en EtOH EtOAc (50 50ml) se redujo con hidrogeno sobre 10% paladio/carbono (800mg) Luego de extraer por filtracion el catalizador y lavar con EtOH, la evaporacion del filtrado produjo el compuesto del titulo como un sólido marron (rendimiento cuantitativo) NMR ($CDCl_3$) 2 96 (t, 4H), 3 55 (brs, 2H), 3 84 (t, 4H), 6 41 (d/s, 2H), 6 79 (t, 1H), m/z 197

Método 23

Sal bicarbonato de *N*-(3-fluoro-4-morfolinofenil)guanidina

3-Fluoro-4-morfolinoanilina (Método 22, 7 8g, 39 8mmol) y cianamida (2 1g, 50mmol) se agitaron en 1,4-dioxano EtOH (75 7 5ml) 4N HCl en 1,4-dioxano (11 9ml, 47 6mmol) se agrego lentamente antes de calentar a 95°C por 6 horas La mezcla de reaccion se evaporo bajo presion reducida y el residuo se trituro con éter El solido resultante se trató con agua (35ml) y se agito durante la lenta adicion de solucion de bicarbonato de sodio acuoso saturado (60ml) El solido se recogió por filtración, se lavo con agua fria (10ml), luego acetona (2x25ml) y aire para producir el compuesto del titulo (10 9g 91%) NMR 2 90 (t, 4H), 3 72 (t, 4H), 5 24 (brs, 4H), 6 52 (d/s, 1H), 6 54 (t, 1H), 6 87 (t, 1H), m/z 239

Metodo 24

1-Acetil-4-(2-cloro-4-nitrofenil)piperazina

2-Cloro-1-fluoro-4-nitrobenceno (10g, 57mmol) y 1-acetilpiperazina (14 6g, 114mmol) se calentaron ordenadamente a 55°C por 1 hora Luego la mezcla de reacción se dejo enfriar a temperatura de la sala La solucion anaranjada viscosa se diluyo con EtOAc y agua Los organicos se lavaron con agua (3 veces), salmuera, se secaron, y la evaporacion del disolvente produjo un aceite anaranjado, que se trituro con isohexano Luego de la evaporacion del disolvente, el compuesto del titulo se obtuvo como un solido amarillo, que se seco de un dia para otro en un horno de vacio a

50°C, (15 68g, 97%) Este se utilizo sin purificación posterior NMR (400 MHz) 2 03 (d, 3H), 3 18 (dt, 4H), 3 62 (m, 4H), 7 30 (d, 1H), 8 17 (dd, 1H), 8 26 (d, 1H), m/z 284-286

Método 25

1-Acetil-4-(2-metil-4-nitrofenil)piperazina

Ttetrafluoroborato de 1-butil-3-metilimidazolio (1 75g, 7 74mmol) se agrego a una solucion agitada de 1-fluoro-2-metil-4-nitrobenceno (12g, 77 35mmol) y 1-acetilpiperazina (39 7g, 309 4mmol) en acetonitrilo (3ml) La mezcla de reaccion se calento entonces a 95°C de un dia para otro La mezcla de reaccion se dejo enfriar a temperatura de la sala La solucion se diluyo con EtOAc y agua El precipitado formado se extrajo por filtracion para producir un solido correspondiente al producto requerido Los orgánicos se lavaron con agua (4 veces), salmuera, se secaron y la evaporación del disolvente para producir un solido Ambos solidos se combinaron y después de triturar con isohexano/eter y filtracion, el compuesto del titulo se obtuvo como un sólido amarillo, el cual se seco en un horno de vacio de un dia para otro a 50°C, (19 61g, 96%) NMR (400MHz) 2 06 (s, 3H), 2 38 (s, 3H), 2 99 (dt, 4H), 3 61 (m, 4H), 7 14 (d, 1H), 8 04 (dd, 1H), 8 07 (d, 1H), m/z 264

Método 26

1-Acetil-4-(2-fluoro-4-nitrofenil)piperazina

Una solucion agitada de 1-(2-fluoro-4-nitrofenil)piperazina (15g, 66 6mmol) en DCM (160ml) se enfrió a 0°C En seguida se agrego trietilamina (11 23ml, 79 92 mmol) seguida por la adicion gota a gota de cloruro de acetilo (5 68ml, 79 92 mmol) La solucion se dejo calentar a temperatura ambiente y agitar por 1 5 horas La mezcla de reaccion se diluyo con DCM, se lavo con agua, bicarbonato de sodio saturado y salmuera Se seco y el disolvente se evaporó para producir el compuesto del titulo como un sólido, el cual se seco en un horno de vacio de un dia para otro a 50°C (17 46g, 98%) NMR(400MHz) 2 05 (s, 3H), 3 30 (dt, 4H,

bajo señal H_2O), 3 61 (m, 4H), 7 18 (t, 1H), 8 02 (d, 1H), 8 02 (dd, 1H), m/z 268

Método 27

(3R,5S)-3,5-Dimetil-1-(4-nitrofenil)piperazina

1-Fluoro-4-nitrobenceno (10g, 70 87mmol) y (2*R*,6*S*)-2,6-dimetilpiperazina (17g, 148 83mmol) se calentaron en acetonitrilo (25ml) a 70°C por 2 horas La solucion se concentró *in vacuo*, luego el residuo se repartió en porciones entre DCM y agua + bicarbonato de sodio saturado El extracto orgánico se lavo con agua (4 veces), salmuera, se seco y se concentró para producir el compuesto del titulo como un solido amarillo, el cual se seco en un horno de vacio de un día para otro a 50°C (16 13g, 97%) NMR (400MHz) 1 04 (d, 6H), 2 39 (m, 2H), 2 77 (m, 2H), 3 89 (dd, 2H), 7 02 (d, 2H), 8 03 (d, 2H), m/z 236

Método 28

(2*S*,5*R*)-2,5-Dimetil-1-(4-nitrofenil)piperazina

1-Fluoro-4-nitrobenceno (6g, 42 52mmol) y (2*R*,5*S*)-2,5-dimetilpiperazina (21 9g, 191 34mmol) se calentaron en acetonitrilo (20ml) a 100°C por 11 horas La solucion se concentró *in vacuo*, luego el residuo se repartio en porciones entre DCM y agua + bicarbonato de sodio saturado El extracto organico se lavó con agua (4 veces), salmuera, se secó y se concentró Cromatografía en gel de silice con MeOH DCM (1 99 a 5 95) produjo el compuesto del título como un aceite, el cual se solidificó al reposar de un día para otro (8 32g, 83%) NMR (400 MHz) 1 08 (d, 3H), 1 16 (d, 3H), 2 55 (dd, 1H), 3 18 (m, 2H), 3 34 (m, 2H), 3 95 (m, 1H), 6 91 (d, 2H), 8 03 (d, 2H), m/z 236

Método 29

(2*R*,6*S*)-1-Acetil-2,6-dimetil-4-(4-nitrofenil)piperazina

El compuesto del titulo se preparó de (3*R*,5*S*)-3,5-dimetil-1-(4-nitrofenil)piperazina (Método 27, 16g, 68 027mmol) y cloruro de acetilo

(8 22ml, 115 65mmol) por el procedimiento de Metodo 26 Se obtuvo como un solido, el cual se seco en un horno de vacio de un dia para otro a 50°C (20 5g, 109%, contaminado con disolvente) NMR (400MHz) 1 19 (brd, 6H), 2 08 (s, 3H), 3 21 (brd, 2H), 4 00 (d, 2H), 4 34 (v brs, 2H), 7 08 (d, 2H), 8 06 (d, 2H), m/z 278

Método 30

(2*R*,5*S*)-1-Acetil-2,5-dimetil-4-(4-nitrofenil)piperazina

El compuesto del titulo se preparó de (2*S*,5*R*)-2,5-dimetil-1-(4-nitrofenil)piperazina (Método 28, 8 22g, 34 95mmol) y cloruro de acetilo (4 5ml, 62 91) por el procedimiento de Metodo 26 Se obtuvo como un aceite, el cual se solidificó al reposar de un dia para otro (11 39g, > 100%, contaminado con disolvente) NMR (400MHz) 1 13 (m, 6H), 3 07 (m, 1H), 3 33 (m, 1H), 3 68 (m, 1H), 4 25 (m, 2H), 4 69 (m, 1H), 7 00 (d, 2H), 8 05 (d, 2H), m/z 278

Método 31

Sal bicarbonato de *N*-[4-(4-acetilpiperazin-1-il)-3-metilfenil]guanidina

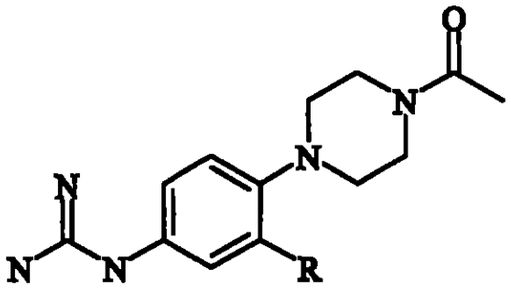
1-Acetil-4-(2-metil-4-nitrofenil)piperazina (Método 25, 19 5g, 74 06 mmol) en EtOH (400ml) se hidrogeno sobre 10% Pd / carbono (2 g) a temperatura y presion ambiente El catalizador se extrajo por filtracion, se lavó con EtOH (500 ml) y la evaporación bajo presión reducida para producir la anilina como un solido crema/purpura, el cual se seco en un horno de vacio de un dia para otro a 50°C, (17g, 98%)

La anilina (15 5 g, 66 44 mmol) se agitó en 1,4-dioxano seco (120 ml) y EtOH (20 ml) 4N HCl en dioxano (19 93 ml, 79 73 mmol) se agrego entonces seguido por cianamida (4 5 g, 106 3mmol) La reaccion se calento a 100°C por 2 5 horas bajo nitrogeno, en seguida se agrego mas cianamida (838 mg, 19 93mmol) y la reacción se calentó por 5 horas mas Luego de la evaporacion bajo presión reducida, la goma solida se trituro con eter y el disolvente se re-evaporó La goma solida se disolvio en agua (volumen pequeño), se agrego lentamente un exceso de solucion de bicarbonato de

sodio saturado con agitacion Luego de 1 hora, el solido se recogio por filtración y se seco en un horno de vacio de un dia para otro a 60°C para producir el compuesto del titulo (20 07g, 90%) NMR (400MHz) 2 04 (s, 3H), 2 22 (s, 3H), 2 75 (dt, 4H), 3 30 (brs, 2H, bajo señal H_2O), 3 56 (m, 4H), 5 97 (v brs, 3H), 6 66 (dd, 1H), 6 70 (d, 1H), 6 90 (d, 1H), m/z 276

Métodos 32-33

Los siguientes compuestos se prepararon por el procedimiento de Método 31 usando el compuesto nitro apropiado



Mét	R	NMR (400MHz)	m/z	SM
32[1]	Cl	2 05 (s, 3H), 2 85 (dt, 4H), 3 29 (s, 1H, bajo señal H_2O), 3 57 (m, 4H), 5 13 (s, 3H), 6 68 (dd, 1H), 6 79 (d, 1H), 6 98 (d, 1H)	296-298	Metodo 24
33[2]	F	2 03 (s, 3H), 2 87 (dt, 4H), 3 29 (s, 2H, under H_20 signal), 3 56 (m, 4H), 5 15 (brs, 3H), 6 53 (m, 2H), 6 87 (t, 1H)	280	Metodo 26

[1] Únicamente se utilizo 1 4 equivalente de cianamida, no se agrego mas y solo se calentó durante 5 5 horas Preparacion de la base libre sal disuelta en una pequeña cantidad de agua seguida por la adición de NaOH acuoso (2 5M) (~22ml) El precipitado formado se extrajo por filtracion para producir un sólido amarillo oscuro, el cual se seco en un horno de vacio de un dia para otro a 50°C, (13 34g, 100%)

[2] Se agregaron mas cianamida y HCl y se dejaron calentar de un dia para otro (14 14g, 68%)

Método 34

N-[4-((3*R*,5*S*)-4-Acetil-3,5-dimetilpiperazin-1-il)fenil]guanidina

El compuesto del titulo se preparo de (2*R*,6*S*)-1-acetil-2,6-dimetil-4-(4-nitrofenil)piperazina (Metodo 29, 16 44g, 66 5mmol) y cianamida (5 03g, 119 7mmol) por el procedimiento de Metodo 31 y calentando de un dia para otro a 95°C La sal bicarbonato se seco en un horno de vacio a 60°C de un dia para otro Como estaba aun humeda, se redisolvio en MeOH y acetona y la evaporacion del disolvente produjo el compuesto del titulo como un solido marron (18 6g, 80%) NMR (400MHz) 1 3 (brs, 6H), 2 05 (s, 3H), 2 70 (brd, 2H), 3 35 (m, 4H bajo señal H_2O), 3 90- 4 60 (v brs, 2H), 5 50-6 40 (v brs, 2H), 6 75 (d, 2H), 6 85 (d, 2H), m/z 290

Método 35

N-[4-((2*S*,5*R*)-4-Acetil-2,5-dimetilpiperazin-1-il)fenil]guanidina

El compuesto del titulo se preparo de (2*R*,5*S*)-1-acetil-2,5-dimetil-4-(4-nitrofenil)piperazina (Metodo 30, 6 5g, 26 29mmol) y cianamida (2 43g, 57 84mmol) por el procedimiento de Método 31 y calentando por 10 horas a 95°C La sal bicarbonato se secó en un horno de vacio a 60°C de un dia para otro Se obtuvo como un sólido (10 23g, > 100% contaminado con disolvente) M/z 290

Método 36

1-(4-Nitrofenil)-azetidin-3-ol

Una mezcla agitada de 4-fluoro-nitrobenceno (12 70g, 90mM), clorhidrato de 3-hidroxiazetidina (10 85g, 99mM) y carbonato de potasio anhidro en acetonitrilo (250ml) se calentó bajo reflujo por 6 horas Al enfriar, ocurrio cierta cristalizacion La mezcla de reaccion se diluyo a 1 41 con agua y el material cristalizado se extrajo por filtración, se lavó con agua y se secó El compuesto del titulo fue un solido cristalino amarillo (14 8g, 85%) NMR 3 73 (m, 2H), 4 25 (m, 2H), 4 60 (m, 1H), 5 77 (d, 1H), 6 43 (d, 2H), 8 00 (d, 2H), m/z 195

Método 37

1-(4-Aminofenil)azetidin-3-ol

Una solucion agitada de 1-(4-nitrofenil)-azetidin-3-ol (Metodo 36, 15 15g, 87mM) en EtOH (250ml) se hidrogeno sobre 10% Pd/C (1 5g) por 18 horas a presion atmosferica. La mezcla de reaccion se filtro y el filtrado se evaporo y se trituro con eter produciendo el compuesto del titulo como un solido cristalino gris Gran parte del producto se habia precipitado de la mezcla de reacción y se habia extraido por filtracion con el catalizador Esto se agito con DMF (100ml) por 15 minutos y el catalizador se extrajo por filtracion El filtrado se evaporó (Hi-Vac) y se trituro con un poco de EtOH La segunda cosecha de producto se extrajo por filtracion, se lavo con eter y se seco NMR 3 35 (m + agua, 2H), 3 90 (t, 2H), 4 32 (s, 2H), 4 45 (m, 1H), 5 41 (d, 1H), 6 20 (d, 2H), 6 45 (d, 2H), m/z 165

Método 38

di-*terc*-Butil((*E*)-{[4-(3-hidroxiazetidin-1-il)fenil]amino}metililiden) biscarbamato

A una solucion de *terc*-butil ester de acido {[(Z)-*terc*-butoxicarbonilimino]-trifluorometanesulfonil-metil}-carbamico (13 62g, 34 8mM) y trietilamina (4 9ml, 34 8mM) en DCM seco (183ml) se agregó1-(4-aminofenil)azetidin-3-ol (Metodo 37, 6 0g, 36 5mM) La solucion se agito a temperatura de la sala bajo nitrogeno por 48 horas La mezcla de reaccion se diluyó con más DCM y se lavó con agua (dos veces), solución de bicarbonato de sodio saturado (dos veces), agua y cloruro de sodio saturado La solucion se seco entonces con sulfato de sodio anhidro, se filtró y se evaporo El producto crudo se trituro con eter/isohexano (2 1), se filtro y se lavo con el mismo disolvente y se seco para producir el compuesto del titulo como un solido amarillo (11 77g, 83%) NMR 1 4 (s, 9H), 1 5 (s, 9H), 3 47 (t, 1H), 4 02 (t, 2H), 4 5 (m, 1H), 5 55 (d, 1H), 6 38 (d, 2H), 7 23 (d, 2H), 9 75 (s, 1H), 11 46 (m, 1H), m/z 407

Metodo 39

Sal bicarbonato de *N*-[4-,3-hidroxiazetidin-1-il)fenilguanidina

Una solucion de di-*terc*-butil ((*E*)-{[4-(3-hidroxiazetidin-1-il)fenil] amino}metililiden)biscarbamato (Método 38, 250mg, 0 62mM) en TFA (4 5 ml) y agua (0 52 ml) se agitó a temperatura de la sala de un dia para otro El agua y el exceso de TFA se eliminaron *in vacuo* La sal cruda se disolvio en MeOH (5ml) y se trató con resina de carbonato de poliestireno macroporoso (0 49g de capacidad 3 0 m equivalente por g), se agrego reactivo en un soporte solido y la mezcla se agito suavemente a temperatura de la sala por 4 horas La resina se extrajo por filtración y se lavo con MeOH y el filtrado se evaporo para producir el compuesto del titulo como un vidrio marrón (45mg, 77%) NMR 3 47 (t, 2H), 4 05 (t, 2H), 4 54 (m, 1H), 6 42 (d, 2H), 7 0 (d, 2H), m/z 207

Método 40

terc-Butil [(3*R*)-1-(4-nitrofenil)pirrolidin-3-il]carbamato

terc-Butil (3*R*)-pirrolidin-3-ilcarbamato (4 54g, 24 4mmol), 4-fluoronitrobenceno (3 78g, 24 mmol) y carbonato de potasio (3 54g 25 6 mmol) en acetonitrilo (70ml) se calentaron bajo reflujo por 18 horas Luego de la evaporación bajo presión reducida, la mezcla se disolvio en DCM (200ml), y se lavo con agua (100ml) y solución de cloruro de sodio saturado (25ml) La solucion se secó y se filtró Luego de la evaporacion bajo presion reducida, cromatografía en gel de sílice eluyendo con DCM produjo el compuesto del titulo (7 19g, 97%) NMR 1 39 (s, 9H), 1 87-1 98 (m, 1H), 2 09-2 21 (m, 1H), 3 15-3 23 (m, 1H), 3 32-3 44 (m, 1H), 3 45-3 51 (m, 1H), 3 53-3 61 (m, 1H), 4 09-4 21 (m, 1H), 6 57 (d, 2H), 7 21 (s, 1H), 8 01 (d, 2H), m/z (MH^+-C_4H_8) 252

Método 41

Sal trifluoroacetato de (3*R*)-(4-Nitrofenil)pirrolidin-3-amina

terc-Butil [(3*R*)-1-(4-nitrofenil)pirrolidin-3-il]carbamato (Metodo 40, 1 0g, 3 26 mmol) en DCM (15ml) se hizo reaccionar con TFA (7 5 ml) a temperatura de la sala por 18 horas El verter en eter frio (200ml) produjo

con filtracion el compuesto del titulo (0 97g, 93%) NMR 2 03-2 17 (m, 1H), 2 22-2 44 (m, 1H), 3 40-3 60 (m, 3H), 3 68-3 74 (m, 1H), 3 95-4 08 (m, 1H), 6 66 (d, 2H), 8 08 (d, 2H), 8 14 (s, 2H)

Metodo 42

N-[(3*R*)-1-(4-Nitrofenil)pirrolidin-3-il]acetamida

Sal trifluoroacetato de (3*R*)-1-(4-nitrofenil)pirrolidin-3-amina (Metodo 41, 0 96g, 3mmol) y acetato sódico (0 245g, 3 mmol) en acido acético (10ml) se hicieron reaccionar con anhidrido de sodio (0 57 ml, 6 mmol) por 18 horas a temperatura de la sala Luego de filtrar y lavar se produjo el compuesto del título como un sólido amarillo (0 63g, 84%) NMR 1 79 (s, 3H), 1 85- 1 98 (m, 1H), 2 09-2 23 (m, 1H), 3 19-3 30 (m, 1H), 3 39-3 52 (m, 2H), 3 55-3 67 (m, 1H), 4 30-4 43 (m, 1H), 6 60 (d, 2H), 8 04 (d, 2H), 8 15 (d, 1H), m/z 250

Método 43

Monoclorhidrato de *N*-[(3*R*)-1-(4-Aminofenil)pirrolidin-3-il]acetamida

N-[(3*R*)-1-(4-nitrofenil)pirrolidin-3-il]acetamida (Metodo 42, 4 5g, 18 mmol) se hidrogeno sobre 10% paladio/carbono a temperatura de la sala y presion de 1 atmósfera en alcohol absoluto (200ml) Luego de la filtración del catalizador y la evaporación a presion reducida se produjo la *N*-[(3*R*)-1-(4-aminofenil)pirrolidin-3-il]acetamida como un solido rojo (3 75g, 95%) NMR ($CDCl_3$) 1 97 (s, 3H), 1 89-2 03 (m, 1H), 2 22-2 34 (m, 1H), 2 54 (s, 2H), 3 06-3 27 (m, 2H), 3 34-3 48 (m, 2H), 4 52-4 68 (m, 1H), 5 79 (brs, 1H), 6 48 (d, 2H), 6 69 (d, 2H), m/z 220 El tratamiento con 4M de cloruro de hidrógeno en 1,4-dioxano produjo el compuesto del titulo (4 21g, 96%) LCMS m/z 220

Método 44

di-*terc*-Butil [(*E*)-({4-[(3*R*)-3-(acetilamino)pirrolidin-1-il]fenil}amino) metililiden]biscarbamato

Monoclorhidrato de *N*-[(3*R*)-1-(4-aminofenil)pirrolidin-3-

ıl]acetamıda (Método 43, 2 47g, 9 67 mmol) y base de Hünig (2 02ml, 1 16 mmol) se hicieron reaccionar con dı-*terc*-butıl [(*Z*)-1*H*-pırazol-1-ılmetılıeden]bıscarbamato (2 95g, 9 5 mmol) en THF (50ml) a temperatura de la sala por 72 horas Luego de la evaporación bajo presión reducida, cromatografía en gel de sılice con EtOAc/ısohexane (50 50 a 100) produjo el compuesto del tıtulo como un solıdo amarıllo (3 06g, 69%) NMR 1 39 (s, 9H), 1 52 (s, 9H), 1 81 (s, 3H), 1 82-1 93 (m, 1H), 2 11-2 24 (m, 1H), 3 00-3 08 (m, 1H), 3 21-3 51 (m, 3H), 4 29-4 40 (m, 1H), 6 50 (d, 2H), 7 29 (d, 2H), 8 12 (d, 1H), 9 74 (s, 1H), 11 49 (s, 1H), m/z 462

Metodo 45

Carbonato de 4-((3*R*)-acetamıdopırrolıdın-1-ıl)fenılguanıdına

[(*E*)-({4-[(3*R*)-3-(acetılamıno)pırrolıdın-1-ıl]fenıl}amıno) metılıeden]bıscarbamato (Metodo 44, 3 06g, 6 6 mmol) se hızo reaccionar con TFA (20ml) en DCM (100ml) a temperatura de la sala bajo nıtrogeno por 18 horas Luego de la evaporación bajo presion reducıda, el resıduo se dısolvıo en MeOH (40ml) y se trato resına de carbamato de polıestıreno macroporoso (0 49g de capacıdad 3 0 m equıvalente por g) (6g), y se agıto por 4 horas La mezcla se filtró y se lavo con MeOH La evaporacion bajo presion reducıda produjo el compuesto del título como un solıdo grıs (1 25g, 65%) NMR 1 80-1 94 (m, 1H), 1 83 (s, 3H), 2 09-2 22 (m, 1H), 2 96-3 09 (m, 1H), 3 19-3 29 (m, 1H), 3 30-3 39 (m, 1H), 3 40-3 52 (m, 1H), 4 28-4 41 (m, 1H), 6 52 (d, 2H), 6 91 (d, 2H), 7 32 (brs, 4H), 8 13 (d, 1H), m/z 262

Metodo 46

terc-Butıl [(3*S*)-1-(4-nıtrofenıl)pırrolıdın-3-ıl]carbamato

El compuesto del tıtulo se preparo por el procedımıento de Metodo 40 a partır de *terc*-butıl (3*S*)-pırrolıdın-3-ılcarbamato (6 11g, 74%) NMR 1 36 (s, 9H), 1 83-1 98 (m, 1H), 2 08-2 20 (m, 1H), 3 12-3 24 (m, 1H), 3 31-3 51 (m, 2H), 3 52-3 65 (m, 1H), 4 09- 4 23 (m, 1H), 6 58 (d, 2H), 7 20 (s, 1H), 8 01 (d, 2H), m/z 198 (MH^+-C_4H_8)

Metodo 47

Sal trifluoroacetato de (3*S*)-1-(4-nitrofenil)pirrolidin-3-amina

El compuesto del titulo se preparo por el procedimiento de Metodo 41 a partir de *terc*-butil [(3*S*)-1-(4-nitrofenil)pirrolidin-3-il]carbamato (Metodo 46) (6 6g, 100%) NMR 2 03-2 19 (m, 1H), 2 20-2 40 (m, 1H), 3 25-3 75 (m, 3H), 3 94-4 04 (m, 1H), 4 38 (brs, 2H), 6 64 (d, 2H), 8 08 (d, 2H), 8 24 (s, 3H) m/z 208

Método 48

N-[(3*S*)-1-(4-Nitrofenil)pirrolidin-3-il]acetamida

El compuesto del titulo se preparó por el procedimiento de Metodo 42 a partir de sal trifluoroacetato de (3*S*)-1-(4-nitrofenil)pirrolidin-3-amina (Metodo 47) (4 2g, 93%) NMR 1 80 (s, 3H), 1 86-1 98 (m, 1H), 2 11-2 24 (m, 1H), 3 15-3 28 (m, 1H), 3 37-3 55 (m, 2H), 3 64-3 70 (m, 1H), 4 32-4 44 (m, 1H), 6 61 (d, 2H), 8 04 (d, 2H), 8 15 (d, 1H) m/z 250

Método 49

N-[(3*S*)-1-(4-Aminofenil)pirrolidin-3-il]acetamida

El compuesto del titulo se preparo por el procedimiento de Metodo 43 a partir de *N*-[(3*S*)-1-(4-nitrofenil)pirrolidin-3-il]acetamida (Método 48) NMR 1 79 (s, 3H), 1 69-1 88 (m, 1H), 2 07-2 20 (m, 1H), 2 82-2 93 (m, 1H), 3 01-3 14 (m, 1H), 3 16-3 38 (m, 2H), 4 25-4 36 (m, 1H), 6 31 (d, 2H), 6 51 (d, 2H), 8 08 (d, 1H) + EtOH

Metodo 50

di-*terc*-Butil [(*E*)-({4-[(3*R*)-3-(acetilamino)pirrolidin-1-il]fenil}amino) metilieden]biscarbamato

El compuesto del titulo se preparó por el procedimiento de Método 44 a partir de *N*-[(3*S*)-1-(4-aminofenil)pirrolidin-3-il]acetamida (Metodo 49) (4 16g, 45%) NMR 1 31- 1 56 (brs, 18H), 1 80 (s, 3H), 1 82-1 93 (m, 1H), 2 07-2 21 (m, 1H), 3 00-3 08 (m, 1H), 3 19-3 40 (m, 2H), 3 43-3 49

(m, 1H), 4 30-4 41 (m, 1H), 6 50 (d, 2H), 7 26 (d, 2H), 7 57 (s, 2H), 8 10 (d, lH), m/z 462

Metodo 51

Carbonato de 4-((3*S*)-acetamidopirrolidin-1-il)fenilguanidina

El compuesto del titulo se preparó por el procedimiento de Metodo 45 a partir de di-*terc*-butil [(*E*)-({4-[(3*R*)-3-(acetilamino)pirrolidin-1-il] fenil}amino)metilieden]biscarbamato (Método 50) (2 26g, 86%) NMR 1 79 (s, 3H), 1 79-1 89 (m, 1H), 2 09-2 21 (m, 1H), 2 97-3 02 (m, 1H), 3 16-3 23 (m, 1H), 3 27-3 44 (m, 3H), 4 26-4 37 (m, 1H), 6 20-6 25 (m, 1H), 6 46 (d, 2H), 6 79 (d, 2H), 7 57 (d, 2H), 8 09 (d, 1H), m/z 262

Método 52

Dimetilamida de ácido (*R*)-1-(4-nitro-fenil)-pirrolidin-2-carboxilico

4-Fluoronitrobenceno (0 47 g, 3 34 mmol), carbonato de potasio (1 39, 10 mmol) y dimetilamida de ácido (R)-pirrolidin-2-carboxilico (0 50, 3 52mmol) se pre-mezclaron en acetonitrilo (40 ml) y se calentaron a reflujo por 36 horas La reaccion se extinguió con cloruro de amonio saturado (40 ml), se extrajo con DCM (2 x 100 ml), se seco y el disolvente se retiro *in vacuo* para producir el compuesto del titulo como un solido amarillo Se agregó éter y el solido se agito, se filtro y se seco (0 85g, 96%) M/z 264

Método 53

Dimetilamida de acido (*S*)-1-(4-amino-fenil)-pirrolidin-2-carboxilico

Dimetilamida de ácido (*R*)-1-(4-nitro-fenil)-pirrolidin-2-carboxilico (Metodo 52, 0 85g) se disolvió en MeOH (50 ml), a esto se agrego formiato de amonio (1 0 g, 16 mmol) y paladio (0 1 g) La reaccion se calento a reflujo por 60 minutos (reaccion descolorada) Se retiro MeOH *in vacuo* y se agrego cloruro de amonio saturado (50 ml) El sistema se extrajo con DCM (2x100 ml), se seco y el disolvente se retiró *in vacuo* para producir el compuesto del titulo como una goma marrón (0 67g, 87%) Rapidamente el

producto se torno oscuro con la exposicion al aire El producto se empleo inmediatamente sin ninguna purificación

Método 54

Dimetilamida de acido (S)-1-(4-guanidino-fenil)-pirrolidin-2-carboxilico

A dimetilamida de acido (*S*)-1-(4-amino-fenil)-pirrolidin-2-carboxilico (Metodo 53, 0 67g) se agregó acetonitrilo (20 ml) y EtOH (2 ml) Se agrego HCl en dioxano (0 86 ml, 3 48 mmol) y la reaccion se agito por 10 minutos, se precipito sal HCl Se agregó cianamida (0 2g, 4 9 mmol) y la reaccion se calento a reflujo durante el fin de semana La reacción negra se filtró y la sal HCl negra se disolvió en agua (5 ml) y se basificó con solución de $NaHCO_3$ (20 ml) No se observo un sólido, la acuosa se basificó aun mas a pH 14 con KOH, se extrajo con DCM (2 x 100 ml), se seco y el disolvente se retiró *in vacuo* para producir el compuesto del titulo como una goma negra (0 50g, 63%) M/z 276

Metodo 55

Acido (*R*)-1-(4-nitro-fenil)-pirrolidin-2-carboxilico

Prolina (3 5g, 30 4 mmol), 4-yodonitrobenceno (7 2g, 28 9mmol), Pd $(PPh_3)_4$ (1 7g, 5mol%), yoduro de cobre (0 3g, 5mol%), cloruro de benciltrietilamonio (11 9g, 52mmol), trietilamina (8 3 ml, 60 mmol) y carbonato de potasio (4 2g, 30 mmol) se pre-mezclaron en DMF (60 ml)/agua (6ml) La reaccion se calento a 80°C por 8 horas Se retiro el DMF *in vacuo* y la goma negra restante se disolvió en DCM, se acidifico con 2 0N HCl (50 ml), se extrajo con DCM (3 x 100 ml), se seco, y el disolvente se retiró *in vacuo* para producir una brea negra La brea se disolvio en una cantidad minima de DCM (7 ml) y se cargo en una columna de silice de 50 g, el sistema se eluyó con 20%EtOAc/isohexano, luego 60% EtOAc/isohexano y finalmente 100% EtOAc El compuesto del titulo se obtuvo como una goma anaranjada NMR (299 954 MHz, $CDCl_3$) 8 13 (d, 2H), 6 52 (d, 2H), 4 41 (d, 1H), 3 66 (t, 1H), 3 49 (q, 1H), 2 47-2 29 (m, 2H), 2 25-2 12 (m, 2H), m/z 237

Método 56

Metilamida de ácido (*R*)-1-(4-nitro-fenil)-pirrolidin-2-carboxílico

A acido (*R*)-1-(4-nitro-fenil)-pirrolidin-2-carboxilico (Metodo 55, 1 8g, 7 6 mmol) en DCM (50 ml) se agregó HATU (3 2g, 8 4 mmol) y DIPEA (2 0ml, 11 4 mmol) La reacción se agito por 10 minutos antes de la adición de metilamina (2 0N in THF, 5 0ml, 15 mmol), la reaccion se agito por 1 hora antes de extinguirla con agua (50ml) La reacción se extrajo con DCM (3 x 100 ml), se seco y el disolvente se retiró *in vacuo* para producir una goma amarilla La purificacion se logro mediante cromatografía de columna eluyendo con 20%EtOAc/isohexano, 60%EtOAc/isohexano y finalmente 100%EtOAc El compuesto del titulo se obtuvo como una goma anaranjada, (1 4g, 74%) NMR (299 954 MHz, $CDCl_3$) 8 10 (d, 2H), 6 56 (d, 2H), 6 24 (s, 1H), 4 20 (t, 1H), 3 75 (t, 1H), 3 40 (q, 1H), 2 80 (d, 3H), 2 36-2 29 (m, 2H), 2 13-2 05 (m, 2H), m/z 250

Método 57

Metilamida de ácido (*R*)-1-(4-amino-fenil)-pirrolidin-2-carboxílico

Metilamida de acido (*R*)-1-(4-nitro-fenil)-pirrolidin-2-carboxilico (Metodo 56, 1 2g, 4 8 mmol) se disolvió en MeOH (50 ml), a esto se agrego formiato de amonio (1 5 g, 24 mmol) y paladio (0 1 g) La reaccion se calentó a reflujo por 60 minutos, la reacción se descoloro Se retiro MeOH *in vacuo* y se agregó cloruro de amonio saturado (50 ml), el sistema se extrajo con DCM (2x100 ml), se seco y el disolvente se retiro *in vacuo* para producir el compuesto del titulo como una goma marrón (1 0g, 95%) El producto se torno rápidamente negro con la exposición al aire El producto se utilizo en forma inmediata sin ninguna purificacion

Metodo 58

1-[4-({(*E*)-{(*terc*-Butoxicarbonil)amino][(*terc*-butoxicarbonil)imino]metil} amino)fenil]-*N*-metil-D-prolinamida

A metilamida de acido (*R*)-1-(4-amino-fenil)-pirrolidin-2-carboxilico

(Metodo 57, 1 0g, 4 5mmol) en DCM (60 ml) se agrego di-*terc*-butil [(*Z*)-1*H*-pirazol-1-ilmetilieden]biscarbamato (1 7g, 5 5 mmol) en una porcion La reaccion se agitó de un dia para otro antes de retirar el disolvente *in vacuo* El residuo se purifico *mediante* cromatografía de columna eluyendo con 20%EtOAc/isohexano, 50%EtOAc/isohexano y finalmente 100%EtOAc El compuesto del título se obtuvo como una espuma blanca (1 9g, 91%)

Método 59

Metilamida de acido (*R*)-1-(4-guanidino-fenil)-pirrolidin-2-carboxilico

A 1-[4-({(E)[(*terc*-butoxicarbonil)amino][(*terc*-butoxicarbonil) imino]metil}amino)fenil]-*N*-metil-D-prolinamida (Metodo 58, 1 9 g) se agregó DCM (60 ml) y TFA (20 ml) La reacción se agitó por 4 horas antes del retiro del disolvente *in vacuo* La reacción se basifico con 2 0N KOH (20 ml) y se extrajo con DCM (2 x 50 ml) El producto no se extrajo en DCM, la capa acuosa se redujo a 90% del volumen inicial y se re-extrajo con DCM (3 x 200 ml), se seco y el disolvente se retiro *in vacuo* para producir el compuesto del titulo como un sólido marron (0 84g, 78%) NMR (299 955 MHz) 7 79 (q, 1H), 7 57 (s, 1H), 7 18 (s, 2H), 7 03 (d, 2H), 6 48 (d, 2H), 3 91 (d, 1H), 3 58-3 54 (m, 1H), 3 17 (q, 1H), 2 56 (d, 3H), 2 19-2 09 (m, 2H), 2 01-1 89 (m, 2H), m/z 261

Método 60

Ciclopropilamida de acido (*R*)-1-(4-nitro-fenil)-pirrolidin-2-carboxilico

A acido (*R*)-1-(4-nitro-fenil)-pirrolidin-2-carboxilico (Metodo 55, 1 8g, 7 6 mmol) en DCM (50 ml) se agrego HATU (3 2g, 8 4 mmol) y DIPEA (2 0ml, 11 4 mmol) La reacción se agito por 10 minutos antes de la adición de metilamina (0 84g, 15 mmol), la reaccion se agito por 1 hora y luego se extinguió con agua (50ml) La reaccion se extrajo con DCM (3 x 100 ml), se secó y el disolvente se retiro *in vacuo* para producir una goma amarilla La purificación se logro mediante cromatografía de columna eluyendo con 20%EtOAc/isohexano, 60% EtOAc/isohexano y finalmente

100%EtOAc El compuesto del titulo se obtuvo como un solido amarillo (1 4g, 74%) NMR (299 954 MHz, $CDCl_3$) δ 8 13 (d, 2H), 6 55 (d, 2H), 6 06 (s, 1H), 4 14 (t, 1H), 3 70 (t, 1H), 3 38 (q, 1H), 2 75-2 66 (m, 1H), 2 36-2 29 (m, 2H), 2 17-1 95 (m, 2H), 0 82-0 73 (m, 2H), 0 46-0 35 (m, 2H), m/z 276

Método 61

Ciclopropilamida de acido (*R*)-1-(4-amino-fenil)-pirrolidin-2-carboxilico

Ciclopropilamida de acido (R)-1-(4-nitro-fenil)-pirrolidin-2-carboxilico (Metodo 60, 142g, 5 1 mmol) se disolvio en MeOH (50 ml), a esto se agrego formiato de amonio (1 6 g, 26 mmol) y paladio (0 1 g) La reaccion se calento a reflujo por 60 minutos, la reaccion se descoloro Se retiro MeOH *in vacuo* y se agrego cloruro de amonio saturado (50 ml), el sistema se extrajo con DCM (2 x 100 ml), se secó y el disolvente se retiró *in vacuo* para producir el compuesto del título como una goma marrón (1 20g, 96%) El producto se torno rapidamente negro con la exposicion al aire El producto se utilizo en forma inmediata sin ninguna purificacion, m/z 246

Método 62

1-[4-({(*E*)-[(*terc*-Butoxicarbonil)amino][*terc*-butoxicarbonil)imino] metil}amino)fenil]-*N*-ciclopropil-D-prolinamida

Ciclopropilamida de acido (*R*)-1-(4-amino-fenil)-pirrolidin-2-carboxilico (Metodo 61, 1 2g, 4 9mmol) en DCM (60 ml) se agrego a di-*terc*-butil [(*Z*)-1*H*-pirazol-1-ilmetilieden]biscarbamato (1 9g, 6 1 mmol) en una porción La reacción se agitó de un día para otro antes del retiro del disolvente *in vacuo* El residuo se purificó mediante cromatografía de columna eluyendo con 20% acetato de etilo/isohexano, 50%EtOAc/isohexano y finalmente 100% EtOAc El compuesto del titulo se obtuvo como una espuma blanca (2 0g, 81%) NMR (299 954 MHz, $CDCl_3$) 11 63 (s, 1H), 10 09 (s, 1H), 7 60 (s, 1H), 7 40 (d, 2H), 6 45 (m, 3H), 3 92 (t, 1H), 3 59 (t, 1H), 3 19 (q, 1H), 2 69 (m, 1H), 2 29-2 22 (m,

2H), 2 03-1 84 (m, 2H), 1 53 (s, 9H), 1 49 (s, 9H), 0 80-0 68 (m, 2H), 0 44-0 32 (m, 2H), m/z 488

Metodo 63

Ciclopropilamida dee acido (*R*)-1-(4-guanidino-fenil)-pirrolidin-2-carboxilico

A 1-[4-({(*E*)-[(*terc*-butoxicarbonil)amino][(*terc*-butoxicarbonil) imino]metil}amino)fenil]-*N*-ciclopropil-D-prolinamida (Metodo 62, 2 0 g) se agregó DCM (60 ml) y TFA (20 ml) La reaccion se agitó por 4 horas antes del retiro del disolvente *in vacuo* A la goma se agrego DCM (75 ml) y un reactivo solido con soporte de resina de carbonato de poliestireno macroporoso (0 49g de capacidad 3 0 m equivalente por g) (20g), la reacción se agitó lentamente de un dia para otro La reacción se filtro y el disolvente se retiró *in vacuo* para producir muy poco producto Se hizo presente un sólido blanco en la copa del filtro, esto se disolvió en MeOH, se agrego igualmente la resina al MeOH, el sistema se agitó por 10 minutos antes de filtrarse, el disolvente se retiró *in vacuo* para producir el compuesto del título como un solido blanco (0 90g, 75%) NMR (299 954 MHz, $CDCl_3$) δ 7 26 (s, 3H), 6 85 (d, 2H), 6 49 (d, 2H), 3 93 (d, 1H), 3 62- 3 60 (m, 1H), 3 17 (q, 1H), 2 70-2 62 (m, 1H), 2 32-2 14 (m, 2H), 2 00-1 92 (m, 2H), 0 76 - 0 63 (m, 2H), 0 42 (q, 2H), m/z 287

Método 64

terc-Butil [(3*R*)-1-(2-fluoro-4-nitrofenil)pirrolidin-3-il]carbamato

El compuesto del titulo se preparo por una ruta analoga a Metodo 40 a partir de *terc*-butil (3*R*)-pirrolidin-3-ilcarbamato (5 40g, 74%) NMR 1 36 (s, 9H), 1 81-1 94 (m, 1H), 2 02-2 16 (m, 1H), 3 30- 3 42 (m, 1H), 3 48-3 59 (m, 1H), 3 69-3 79 (m, H), 4 02- 4 17 (m, 1H), 6 72 (t, 1H), 7 18 (brs, 1H), 7 92 (d, 2H), m/z 270 (MH^+-C_4H_8)

Método 65

Sal trifluoroacetato de (3*R*)-1-(2-fluoro-4-nitrofenil)pirrolidin-3-amina

El compuesto del título se preparó por una ruta analoga a Metodo 41 a partir de *terc*-butil [(3*R*)-1-(2-fluoro-4-nitrofenil)pirrolidin-3-il] carbamato (Metodo 64) (5 12g, 94%) NMR 2 01-2 14 (m, 1H), 2 20-2 36 (m, 1H), 3 53-4 01 (m, 4H), 6 80 (t, 1H), 7 96 (d, 2H), 8 18 (s, 3H), m/z 226

Método 66

N-[(3R)-1-(2-Fluoro-4-nitrofenil)pirrolidin-3-il]acetamida

El compuesto del título se preparo por una ruta analoga a Metodo 42 a partir de sal trifluoroacetato de (3*R*)-1-(2-fluoro-4-nitrofenil)pirrolidin-3-amina (Metodo 65) (3 78g, 90%) NMR 1 80 (s, 3H), 1 85-1 94 (m, 1H), 2 05-2 19 (m, 1H), 3 32-3 42 (m, 1H), 3 51 - 3 71 (m, 2H), 3 73-3 82 (m, H), 4 28-4 36 (m, 1H), 6 72 (t, 1H), 7 38-7 92 (n, 2H), 8 11 (d, 1H), m/z 268

Método 67

N-[(3*R*)-1-(4-Amino-2-fluorofenil)pirrolidin-3-il]acetamida

El compuesto del título se preparo por una ruta análoga a Metodo 43 a partir de *N*-[(3*R*)-1-(2-fluoro-4-nitrofenil)pirrolidin-3-il]acetamida (Metodo 66) (2 62g, 76%) NMR 1 64-1 76 (m, 1H), 1 79 (s, 3H), 2 02-2 16 (m, 1H), 2 87-2 92 (m, H), 2 99-3 05 (m, 1H), 3 16-3 32 (m, 2H), 4 16-4 28 (m, 1H), 4 68 (brs, 2H), 6 22-6 33 (m, 1H), 6 35 (d, 2H), 6 73 (d, 1H), 8 02 (d, H), m/z 238

Metodo 68

di-*terc*-Butil [(*E*)-({2-fluoro-4-[(3*R*)-3-(acetilamino)pirrolidin-1-il]fenil} amino)metilieden]biscarbamato

El compuesto del título se preparo por una ruta análoga a Metodo 44 a partir de *N*-[(3*R*)-1-(4-amino-2-fluorofenil)pirrolidin-3-il]acetamida (Metodo 67) NMR 1 39 (brs, 9H), 1 46 (brs, 9H), 1 79 (s, 3H), 1 70-1 87 (m, 1H), 2 02-2 16 (m, 1H), 3 09-3 16 (m, 1H), 3 22-3 34 (m, 1H), 3 38-3 47 (m, 1H), 3 51-3 56 (m, 1H), 4 25-4 32 (m, 1H), 6 68 (t, 1H), 7 08 (d,

1H), 7 41 (d, 1H), 8 08 (d, 1H), 8 89 (brs, 1H), 9 83 (brs, 1H), 11 41 (brs, 1H), m/z 480

Método 69

Carbonato de 2-fluoro-4-((3*R*)-acetamidopirrolidin-1-il)fenilguanidina

El compuesto del titulo se preparo por una ruta análoga a Método 45 a partir de di-*terc*-butil [(*E*)-({2-fluoro-4-[(3*R*)-3-(acetilamino)pirrolidin-1-il]fenil}amino)metilideno]biscarbamato (Método 68) (2 43g, 86%) NMR 1 75-1 86 (m, 1H), 1 80 (s, 3H), 2 06-2 18 (m, 1H), 3 21-3 38 (m, 2H), 3 50-3 60 (m, 1H), 4 21-4 34 (m, 1H), 6 72 (t, 1H), 6 89 (d, 1H), 7 00 (d, 1H), 7 29 (brs, 3H), 8 08 (d, 1H), 9 50 (s, 1H)

Método 70

Sal trifluoroacetato de 4-((3*R*)-acetamidopirrolidin-1-il)fenilguanidina

Monoclorhidrato de *N*-[(3*R*)-1-(4-aminofenil)pirrolidin-3-il]acetamida (Metodo 44, 3 31g, 15 mmol), di-*terc*-butil [(*Z*)-1*H*-pirazol-1-ilmetilideno]biscarbamato (5 91g, 15 mmol) y trietilamina (4 17 ml, 30 mmol) en DCM (50 ml) se calentaron a 40°C por 18 horas Luego de la evaporacion bajo presion reducida, la cromatografía en gel de silice con acetato de etilo/isohexano (50 50 a 100) produjo di-*terc*-butil [(*E*)-({4-[(3*R*)-3-(acetilamino)pirrolidin-1-il]fenil}amino)metilideno]biscarbamato, el cual se disolvio en DCM (80ml) y se trato con TFA (15 ml) a temperatura ambiente por 18 horas bajo nitrógeno Luego de la evaporación bajo presion reducida, el residuo se disolvió en MeOH (20ml) y se diluyo con eter El compuesto del titulo se recogio por filtracion como un solido blancuzco (1 79g, 30% en dos pasos) NMR 1 80 (s, 3H), 1 81-1 93 (m, 1H), 2 10-2 27 (m, 1H), 2 99-3 06 (m, 1H), 3 19-3 51 (m, 3H), 4 27-4 39 (m, 1H), 6 52 (d, 2H), 7 03 (d, 2H), 7 16 (s, 3H), 8 10 (d, 1H), 9 36 (s, 1H)

Ejemplo 164

Lo siguiente ilustra formulaciones farmaceuticas representativas que contienen el compuesto de fórmula (I), o una sal farmaceuticamente aceptable o su ester hidrolizable *in vivo* (a partir de ahora, compuesto X), para uso terapeutico o profilactico en humanos -

(a) Tableta I	**mg/tableta**
Compuesto X	100
Lactosa Ph Eur	182 75
Croscarmelosa sodica	12 0
Pasta de almidon de maiz (pasta 5% p/v)	2 25
Estearato de magnesio	3 0

(b) Tableta II	**mg/tableta**
Compuesto X	50
Lactosa Ph Eur	223 75
Croscarmelosa sodica	6 0
Almidon de maiz	15 0
Polivinilpirrolidona (pasta 5% p/v)	2 25
Estearato de magnesio	3 0

(c) Tableta III	**mg/tableta**
Compuesto X	1 0
Lactosa Ph Eur	93 25
Croscarmelosa sódica	4 0
Pasta de almidón de maíz (pasta 5% p/v)	0 75
Estearato de magnesio	1 0

(d) Cápsula	**mg/capsula**
Compuesto X	10
Lactosa Ph Eur	488 5
Estearato de magnesio	1 5

(e) Inyección I	**(50 mg/ml)**
Compuesto X	5 0% p/v
1M solucion de hidróxido se sodio	15 0% v/v

0 1M acido clorhidrico	(para ajustar pH a 7 6)
Polietilen glicol 400	4 5% p/v
Agua para inyeccion	a 100%

(f) Inyección II	**10 mg/ml**
Compuesto X	1 0% p/v
Fosfato de sodio BP	3 6% p/v
0 1M solución de hidróxido de sodio	15 0% v/v
Agua para inyección	a 100%

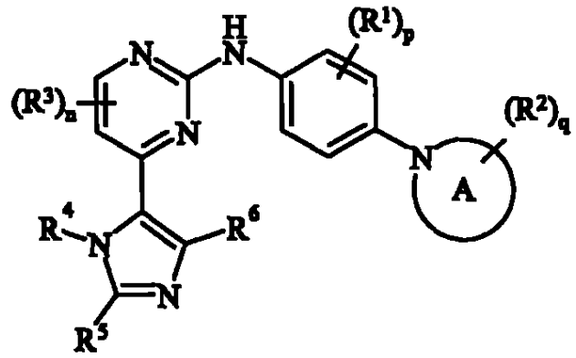
(g) Injección III	**(1mg/ml, tamponada a pH6)**
Compuesto X	0 1% p/v
Fosfato de sodio BP	2 26% p/v
Ácido citrico	0 38% p/v
Polietilen glicol 400	3 5% p/v
Agua para inyección	a 100%

Nota

Las formulaciones anteriores pueden obtenerse por procedimientos tradicionales bien conocidos en el arte farmaceutico Las tabletas (a)-(c) pueden recubrirse con una cubierta gastrorresistente por medios tradicionales, por ejemplo para proporcionar una cubierta de ftalato acetato de celulosa

Reivindicaciones

1 Un compuesto de formula (I)



(I)

en donde

Anillo A es un anillo saturado de 4-7 miembros, enlazado a nitrogeno, que contiene opcionalmente un átomo adicional de nitrogeno, oxigeno o azufre, en donde, si anillo A contiene un atomo de nitrogeno adicional, ese nitrógeno puede sustituirse opcionalmente por R^7,

R^1 es halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, C_{1-6}alquilo, C_{1-6}alcoxi, C_{2-6}alquenilo o C_{2-6}alquinilo,

p es 0-4, en donde los valores de R^1 pueden ser los mismos o diferentes,

R^2 se selecciona de halo, nitro, ciano, hidroxi, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, azido, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcanoilo, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, carbociclil-R^{34}-, heterociclil-R^{35}-, C_{1-6}alquilS(O)$_a$, en donde a es 0 a 2, C_{1-6}alcoxivarbonilo, *N*-(C_{1-6}alquil)sulfamoilo o *N*,*N*- (C_{1-6}alquil)$_2$sulfamoilo, en donde R^2 independientemente puede sustituirse de manera opcional en carbono por uno o más R^8, o R^2 es -NHR^9, -NR^{10}R^{11} o -O-R^{12},

q es 0-2, en donde los valores de R^2 pueden ser los mismos o diferentes,

R^3 es halo, nitro, ciano, hidroxi, trifluorometilo, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-3}alquilo, C_2

$_3$alquenilo, C_{2-3}alquinilo, C_{1-3}alcoxi, C_{1-3}alcanoilo, *N*-(C_{1-3}alquil)amino, *N,N*-(C_{1-3}alquil)$_2$amino, C_{1-3}alcanoilamino, *N*-(C_{1-3}alquil)carbamoilo, *N,N*-(C_{1-3}alquil)$_2$carbamoilo, C_{1-3}alquilS(O)$_a$, en donde a es 0 a 2, *N*-(C_{1-3}alquil)sulfamoilo o *N,N*-(C_{1-3}alquil)$_2$sulfamoilo, en donde R^3 puede sustituirse independientemente de manera opcional en carbono por uno o mas R^{13},

n es 0 a 2, en donde los valores de R^3 pueden ser los mismos o diferentes,

R^4 es hidrogeno, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, carbociclilo o un heterociclilo enlazado a carbono, en donde R^4 puede sustituirse de manera opcional en carbono por uno o mas R^{14}, y en donde, si dicho heterociclilo contiene una fraccion -NH-, ese nitrogeno puede sustituirse opcionalmente por un grupo seleccionado de R^{15},

R^5 y R^6 se seleccionan independientemente de hidrogeno, halo, nitro, ciano, hidroxi, trifluorometoxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquilS(O)$_a$, en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino, C_{3-8}cicloalquilo o un grupo heterociclico saturado de 4-7 miembros, en donde R^5 y R^6 independientemente uno de otro puede sustituirse de manera opcional en carbono por uno o mas R^{16}, y en donde, si dicho grupo heterociclico saturado de 4-7 miembros contiene una fraccion -NH-, ese nitrógeno puede sustituirse opcionalmente por un grupo seleccionado de R^{17},

R^7, R^9, R^{10}, R^{11} y R^{12} se seleccionan independientemente de C_{1-6}alquilo, C_{1-6}alcanoilo, C_{1-6}alquilsulfonilo, C_{2-6}alquenilsulfonilo, C_{2-6}alquinilsulfonilo, C_{1-6}alcoxicarbonilo, carbamoilo, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)carbamoilo, carbociclilo, heterociclilo, carbociclil-R^{18}- o heterociclil- R^{19}-, en donde R^7, R^9, R^{10}, R^{11} y R^{12} pueden sustituirse independientemente de manera opcional en carbono por un grupo

seleccionado de R^{20}, y en donde, si dicho heterociclilo contiene una fracción -NH-, ese nitrógeno puede sustituirse opcionalmente por R^{21},

R^{14} y R^{20} se seleccionan independientemente de halo, nitro, ciano, hidroxi, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, C_{2-6}alqueniloxi, C_{2-6}alquiniloxi, C_{1-6}alcoxiC_{1-6}alcoxi, C_{1-6}alcoxiC_{1-6}alcoxiC_{1-6}alcoxi, C_{1-6}alcanoilo, C_{1-6}alcanoiloxi, *N*-(C_{1-6}alquil)amino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcanoilamino, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, C_{1-6}alquil$S(O)_a$, en donde a es 0 a 2, C_{1-6}alcoxicarbonilo, *N*-(C_{1-6}alquil)sulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino, carbociclilo, heterociclilo, carbociclilC_{1-6}alquil-R^{22}-, heterociclilC_{1-6}alquil-R^{23}-, carbociclil-R^{24}- o heterociclil-R^{25}-, en donde R^{14} y R^{20} puede sustituirse independientemente de manera opcional en carbono por uno o mas R^{26}, y en donde, si dicho heterociclilo contiene una fracción -NH-, ese nitrogeno puede sustituirse opcionalmente por un grupo seleccionado de R^{27},

R^{18}, R^{19}, R^{22}, R^{23}, R^{24}, R^{25}, R^{34} o R^{35} se seleccionan independientemente de -O-, -N(R^{28})-, -C(O)-, -N(R^{29})C(O)-, -C(O)N(R^{30})-, $S(O)_s$-, -SO_2N(R^{31})- o -N(R^{32})SO_2-, en donde R^{28}, R^{29}, R^{30}, R^{31} y R^{32} se seleccionan independientemente de hidrógeno o C_{1-6}alquilo y s es 0-2,

R^{15}, R^{17}, R^{21} y R^{27} se seleccionan independientemente de C_{1-6}alquilo, C_{1-6}alcanoilo, C_{1-6}alquilsulfonilo, C_{1-6}alcoxicarbonilo, carbamoilo, *N*-(C_{1-6}alquil)carbamoilo, *N,N*-(C_{1-6}alquil)carbamoilo, bencilo, benciloxicarbonilo, benzoilo y fenilsulfonilo, en donde R^{15}, R^{17}, R^{21} y R^{27} independientemente uno de otro pueden sustituirse de manera opcional en carbono por uno o más R^{33}, y

R^{8}, R^{13}, R^{16}, R^{26} y R^{33} se seleccionan independientemente de halo, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo,

metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo o *N*-metil-*N*-etilsulfamoilo,
o su sal farmacéuticamente aceptable o éster hidrolizable *in vivo*

2 Un compuesto de formula (I), como se reivindica en la reivindicacion 1 en donde

Anillo A es un anillo saturado de 4-7 miembros, enlazado a nitrogeno, que contiene opcionalmente un atomo adicional de nitrogeno u oxigeno, en donde, si anillo A contiene un átomo adicional de nitrogeno, ese nitrógeno puede sustituirse opcionalmente por R^7, en donde

R^7 se selecciona de C_{1-6}alcanoilo, C_{1-6}alquilsulfonilo, C_{2-6}alquenilsulfonilo, carbociclil-R^{18}- o heterociclil-R^{19}-, en donde R^7 puede sustituirse independientemente de manera opcional en carbono por un grupo seleccionado de R^{20}, y en donde, si dicho heterociclilo contiene una fraccion -NH-, ese nitrógeno puede sustituirse opcionalmente por R^{21},

R^{18} y R^{19} son -C(O)-,

R^{20} se selecciona de halo, ciano, hidroxi, C_{1-6}alcoxi, C_{2-6}alquiniloxi, C_{1-6}alcanoiloxi, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alquilS(O)$_a$, en donde a es 2 o heterociclilo, en donde R^{20} puede sustituirse de manera opcional en carbono por uno o más R^{26},

R^{21} es C_{1-6}alquilo, y

R^{26} es hidroxi,

o su sal farmaceuticamente aceptable o ester hidrolizable *in vivo*

3 Un compuesto de formula (I) como se reivindica en cualquiera de las reivindicaciones 1 o 2 en donde R^1 es halo o C_{1-6}alquilo o su sal farmaceuticamente aceptable o ester hidrolizable *in vivo*

4 Un compuesto de formula (I) como se reivindica en una cualquiera de las reivindicaciones 1-3 en donde p es 0 o 1, o su sal farmaceuticamente aceptable o ester hidrolizable *in vivo*

5 Un compuesto de formula (I) como se reivindica en una cualquiera de las reivindicaciones 1-4 en donde

R^2 se selecciona de hidroxi, amino, azido, C_{1-6}alquilo, *N*-(C_{1-6}alquil)carbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, carbociclil-R^{34}-, -NHR^9 o -O-R^{12},

R^9 y R^{12} se seleccionan independientemente de C_{1-6}alcanoilo o C_{1-6}alquilsulfonilo, en donde R^9 y R^{12} pueden sustituirse independientemente de manera opcional en carbono por un grupo seleccionado de R^{20},

R^{20} es hidroxi, y

R^{34} es -N(R^{29})C(O)-, en donde R^{29} es hidrogeno,

o su sal farmaceuticamente aceptable o ester hidrolizable *in vivo*

6 Un compuesto de formula (I) como se reivindica en una cualquiera de las reivindicaciones 1-5 en donde R^3 es halo o su sal farmaceuticamente aceptable o ester hidrolizable *in vivo*

7 Un compuesto de fórmula (I) como se reivindica en una cualquiera de las reivindicaciones 1-6 en donde n es 0 o 1, o su sal farmaceuticamente aceptable o ester hidrolizable *in vivo*

8 Un compuesto de formula (I) como se reivindica en una cualquiera de las reivindicaciones 1-7 en donde

R^4 es C_{1-6}alquilo o carbociclilo, en donde R^4 puede sustituirse de manera opcional en carbono por uno o mas R^{14}, en donde

R^{14} es carbociclilo,

o su sal farmaceuticamente aceptable o ester hidrolizable *in vivo*

9 Un compuesto de formula (I) como se reivindica en una cualquiera de las reivindicaciones 1-8 en donde

R^5 y R^6 se seleccionan independientemente de hidrogeno o C_{1-6}alquilo, en donde R^5 y R^6 independientemente uno de otro pueden sustituirse de manera opcional en carbono por uno o más R^{16}, en donde

R^{16} se selecciona de metoxi,

o su sal farmaceuticamente aceptable o éster hidrolizable *in vivo*

Un compuesto de fórmula (I), como se describe en la reivindicacion 1, en donde

Anillo A, R^2 y q juntos forman piperazin-1-ilo, morfolino, 4-mesilpiperazin-1-ilo, 4-acetilpiperazin-1-ilo, 4-(2-acetoxiacetil)piperazin-1-ilo, 4-(2-hidroxiacetil)piperazin-1-ilo, 4-(2-cloroacetil)piperazin-1-ilo,4- (2-metoxiacetil)piperazin-1-ilo, (3-metoxipropanoil)piperazin-1-ilo, (3-hidroxi-3-metilbutanoil)piperazin-1-ilo, (3-hidroxi-2,2-dimetilpropanoil) piperazin-1-ilo, ((R)-3-metil-2-hidroxibutanoil)piperazin-1-ilo, ((S)-3-metil-2-hidroxibutanoil)piperazin-1-ilo, 4-(2-dimetilaminoacetil)piperazin-1-ilo, 4-[2-(dimetilamino)etilsulfonil]piperazin-1-ilo, 4-[2-(metoxi)etilsulfonil] piperazin-1-ilo, 4-[2-(hidroxi)etilsulfonil]piperazin-1-ilo, 4-(ciclopropilcarbonil)piperazin-1-ilo, 4-(1-hidroxiciclopropilcarbonil) piperazin-1-ilo, 4-(1-cianociclopropilcarbonil)piperazin-1-ilo, 4-(2-hidroxi-2-metilpropanoil)piperazin-1-ilo, 4-((R)-2-hidroxipropanoil)piperazin-1-ilo, 4-((S)-2-hidroxipropanoil)piperazin-1-ilo, 4-((R)-2-metoxipropanoil) piperazin-1-ilo, 4-((S)-2-metoxipropanoil)piperazin-1-ilo, 4-((R)-tetrahidrofuran-2-ilcarbonil)piperazin-1-ilo, 4-((S)-tetrahidrofuran-2-ilcarbonil)piperazin-1-ilo, 4-(isobutiril)piperazin-1-ilo, 4-((R)-2-hidroxibutanoil)piperazin-1-ilo, 4-((S)-2-hidroxibutanoil)piperazin-1-ilo, (R)-3-acetilaminopirrolidin-1-ilo, (S)-3-acetilaminopirrolidin-1-ilo, (R)-2-(ciclopropilaminocarbonil)pirrolidin-1-ilo, (R)-2-(*N*-metilcarbamoil) pirrolidin-1-ilo, (S)-2-(*N*,*N*-dimetilcarbamoil)pirrolidin-1-ilo, 4-(etenilsulfonil)piperazin-1-ilo, 4-[2-(2-propin-1-iloxi)acetil]piperazin-1-ilo, 4-(tetrahidrofuran-3-ilcarbonil)piperazin-1-ilo, 4-(3-dimetilaminopropanoil) piperazin-1-ilo, 4[2-(*N*-metil-*N*-hidroximetilamino)acetil]piperazin-1-ilo, 4-[3-hidroxi-2-(hidroximetil)propanoil]piperazin-1-ilo, 4-[2-(1,2,3,4-tetrazol-1-il)acetil]piperazin-1-ilo, 4-[2-(1,2,3,4-tetrazol-5-il)acetil]piperazin-1-ilo,

4-(1-metil-L-propil)piperazin-1-ilo, 4-[2-(mesil)acetil]piperazin-1-ilo, 4-(2,2-difluoroacetil)piperazin-1-ilo, 4-[2-(pirrolidin-1-il)acetil]piperazin-1-ilo, 4-[2-(morfolino)acetil]piperazin-1-ilo, 4-[2-(dietilamino)acetil] piperazin-1-ilo, 4-(propionil)piperazin-1-ilo, 4-(3-hidroxipropionil) piperazin-1-ilo, 4-[2-azetidin-1-il)acetil]piperazin-1-ilo, (R)-3-aminopirrolidin-1-ilo, (S)-3-aminopirrolidin-1-ilo, (3*R*,5*S*)-4-acetil-3,5-dimetilpiperazin-1-ilo, (2*S*,5*R*)-4-acetil-2,5-dimetilpiperazin-1-ilo, (2*RS*, 6*SR*)-2,6-dimetilmorfolin-4-il]fenil, 3-hidroxiazetidin-1-ilo, 3-acetilaminoazetidin-1-ilo, 3-(2-hidroxiacetilamino)azetidin-1-ilo, 3-mesilaminoazetidin-1-ilo,3-mesiloxiazetidin-1-ilo, 3-azidoazetidin-1-ilo, 3-aminoazetidin-1-ilo, (3*R*)-3-{[(2*S*)-2-hidroxipropanoil]amino}pirrolidin-1-ilo, (3*S*)-3-{[(2S)-2-hidroxipropanoil]amino}pirrolidin-1-ilo, (3*S*)-3-(glicoloilamino)pirrolidin-1-ilo y (3*R*)-3-(glicoloilamino)pirrolidin-1-ilo

R^1 es fluoro, cloro o metilo,

P es 0 o 1,

R^2 se selecciona de hidroxi, amino, azido, metilo, *N*-metilcarbamoilo, *N*,*N*-dimetilcarbamoilo, acetamido, {[(2*S*)-2-hidroxipropanoil]amino}, glicoloilamino, mesilamino, 2-hidroxiacetamido, mesiloxi o *N*-ciclopropilcarbamoilo

q es 0-2, en donde los valores de R^2 pueden ser los mismos o diferentes,

R^3 es 5-fluoro o 5-cloro,

n es 0 o 1,

R^4 es etilo, isopropilo, isobutilo, ciclobutilo o ciclopropilmetilo,

R^5 y R^6 se seleccionan independientemente de hidrógeno, metilo, etilo, metoximetilo, propilo,

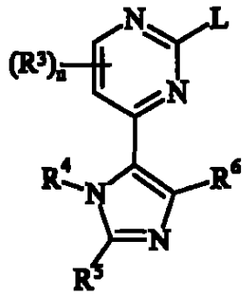
o su sal farmacéuticamente aceptable o éster hidrolizable *in vivo*

11 Un compuesto de formula (I), como se describe en la reivindicacion 1, seleccionado de

2-{4-[4-(2-hidroxiacetil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina clorhidrato,

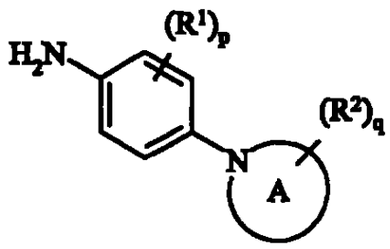
2-{4-[4-(2-hidroxiacetil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina,
(2*S*)-1-[4-(4-{[5-fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il) pirimidin-2-il]amino}fenil)piperazin-1-il]-1-oxopropan-2-ol,
2-[4-(morfolino)anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina
2-{4-[4-(acetil)piperazin-1-il]anilino}-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-5-fluoropirimidina,
2-[4-(4-acetilpiperazin-1-il)anilino]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidina,
5-fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)-*N*-{4-[4-(metoxiacetil) piperazin-1-il]fenil}pirimidin-2-amina,
N-[4-(4-acetilpiperazin-1-il)-3-fluorofenil]-5-fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-amina,
N-[4-(4-acetilpiperazin-1-il)-3-fluorofenil]-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-amina, y
(2*R*)-1-[4-(4-{[5-fluoro-4-(1-isopropil-2-metil-1*H*-imidazol-5-il)pirimidin-2-il]amino}fenil)piperazin-1-il]-1-oxopropan-2-ol,
o su sal farmacéuticamente aceptable o éster hidrolizable *in vivo*

12 Un proceso para preparar un compuesto de fórmula (I), como se reivindica en una cualquiera de las reivindicaciones 1-11, o su sal farmacéuticamente aceptable o éster hidrolizable *in vivo*, proceso que, en donde grupos variables son, a menos que se especifique lo contrario, como se define en la reivindicacion 1, consta de
Proceso a) reacción de una pirimidina de fórmula (II)



(II)

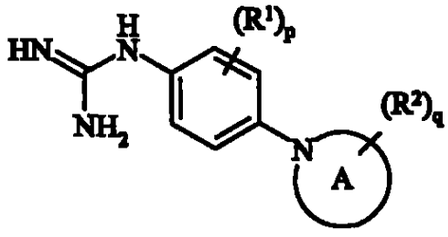
en donde L es un grupo desplazable, con una anilina de fórmula (III)



(III)

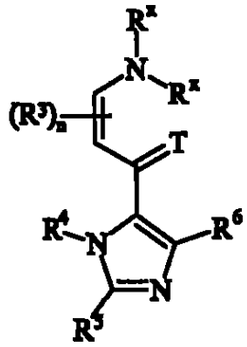
o

Proceso b) hacer reaccionar un compuesto de formula (IV)



(IV)

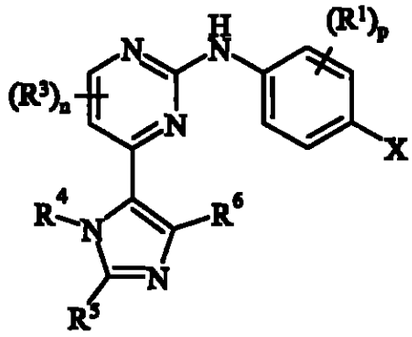
con un compuesto de formula (V)



(V)

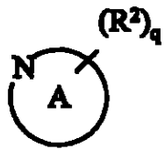
en donde T es O o S, R^x puede ser el mismo o diferente y se selecciona de C_{1-6}alquilo, o

Proceso c) reacción de una pirimidina de formula (VI)



(VI)

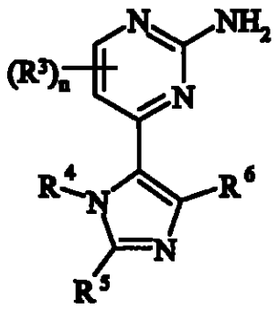
en donde X es un grupo desplazable, con un heterociclilo de formula (VII)



(VII)

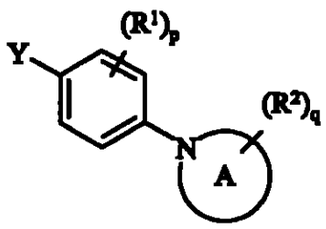
o

Proceso d) para compuestos de formula (I), hacer reaccionar una pirimidina de formula (VIII)



(VIII)

con un compuesto de formula (IX)



(IX)

donde Y es un grupo desplazable,

y, posteriormente, si es necesario

i) convertir un compuesto de la fórmula (I) en otro compuesto de la fórmula (I),

ii) retirar grupos protectores cualesquiera,

iii) formar una sal farmacéuticamente aceptable o éster hidrolizable *in vivo*

13 Una composición farmaceutica que comprende un compuesto de fórmula (I) o su sal farmaceuticamente aceptable o éster hidrolizable *in vivo*, como se reivindica en una cualquiera de las reivindicaciones 1-11, en asociacion con un diluyente o vehiculo farmaceuticamente aceptable

14 Un compuesto de la formula (I), o su sal farmaceuticamente aceptable o ester hidrolizable *in vivo*, como se reivindica en una cualquiera de las reivindicaciones 1-11, para uso en un metodo de tratamiento del cuerpo humano o animal mediante terapia

15 Un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o ester hidrolizable *in vivo*, como se reivindica en una cualquiera de las reivindicaciones 1-11, para uso como medicamento

16 El uso de un compuesto de la formula (I), o su sal farmaceuticamente aceptable o ester hidrolizable *in vivo*, como se reivindica en una cualquiera de las reivindicaciones 1-11, en la fabricacion de un medicamento para uso produccion de un efecto inhibidor del ciclo celular, antiproliferacion celular en un animal de sangre caliente tal como el hombre

17 El uso de un compuesto de la formula (I), o su sal farmaceuticamente aceptable o éster hidrolizable *in vivo*, como se reivindica en una cualquiera de las reivindicaciones 1-11, en la fabricación de un medicamento para uso en el tratamiento de neoplasias malignas (tumores sólidos y leucemias), trastornos de fibroproliferación y diferenciacion, psoriasis, artritis

reumatoide, sarcoma de Kaposi, hemangioma, nefropatias agudas y crónicas, ateroma, arteriosclerosis, restenosis arterial, enfermedades autoinmunitarias, inflamacion cronica y aguda, enfermedades oseas y afecciones oculares con proliferación vascular retiniana, particularmente en el tratamiento de neoplasias malignas

18 El uso de un compuesto de la formula (I), o su sal farmaceuticamente aceptable o ester hidrolizable *in vivo*, como se reivindica en una cualquiera de las reivindicaciones 1-11, en la fabricación de un medicamento para uso en el tratamiento de cáncer

19 El uso de acuerdo con la reivindicacion 18 en donde dicho cancer es leucemia, cáncer de mama, cancer de pulmon, cancer de colon, cancer rectal, cancer del estómago, cancer de próstata, cancer de vejiga, cancer del pancreas, cancer de ovarios, cancer del higado, cancer del riñon, cancer de piel y cancer de la vulva

20 El uso de un compuesto de la formula (I), o su sal farmaceuticamente aceptable o éster hidrolizable *in vivo*, como se reivindica en una cualquiera de las reivindicaciones 1-11, en la fabricacion de un medicamento para uso en la produccion de un efecto inhibidor de CDK

21 Un metodo para producir un efecto inhibidor del ciclo celular, antiproliferación celular en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de formula (I), como se reivindica en una cualquiera de las reivindicaciones 1-11

22 Un método de tratar neoplasias malignas, tumores sólidos y leucemias, trastornos de fibroproliferacion y diferenciación, psoriasis, artritis reumatoide, sarcoma de Kaposi, hemangioma, nefropatias agudas y cronicas, ateroma, arteriosclerosis, restenosis arterial, enfermedades

autoinmunitarias, inflamación cronica y aguda, enfermedades oseas y afecciones oculares con proliferación vascular retiniana, en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de formula (I) o su sal farmacéuticamente aceptable o éster hidrolizable *in vivo*, como se reivindica en una cualquiera de las reivindicaciones 1-11

23 Un método de tratar cancer en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de formula (I) o su sal farmaceuticamente aceptable o ester hidrolizable *in vivo*, como se reivindica en una cualquiera de las reivindicaciones 1-11

24 Un metodo como se reivindica en la reivindicacion 23 en donde dicho cancer es leucemia, cáncer de mama, cancer de pulmon, cancer de colon, cáncer rectal, cancer del estomago, cáncer de prostata, cáncer de vejiga, cancer del páncreas, cáncer de ovarios, cancer del higado, cancer del riñon, cáncer de piel y cancer de la vulva

25 Un metodo de producir un efecto inhibidor de CDK en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I) o su sal farmaceuticamente aceptable o ester hidrolizable *in vivo*, como se reivindica en una cualquiera de las reivindicaciones 1-11

26 Una composicion farmaceutica que comprende un compuesto de la formula (I), o su sal farmaceuticamente aceptable o ester hidrolizable *in vivo*, como se reivindica en una cualquiera de las reivindicaciones 1-11, en asociación con un diluyente o vehiculo farmaceuticamente aceptable para uso en la produccion de un efecto inhibidor del ciclo celular,

antiproliferacion celular en un animal de sangre caliente tal como el hombre

27 Una composición farmaceutica que comprende un compuesto de la formula (I), o su sal farmacéuticamente aceptable o ester hidrolizable *in vivo*, como se reivindica en una cualquiera de las reivindicaciones 1-11, en asociacion con un diluyente o vehiculo farmaceuticamente aceptable para uso en el tratamiento de neoplasias malignas, tumores solidos y leucemias, trastornos de fibroproliferación y diferenciacion, psoriasis, artritis reumatoide, sarcoma de Kaposi, hemangioma, nefropatias agudas y cronicas, ateroma, arteriosclerosis, restenosis arterial, enfermedades autoinmunitarias, inflamación cronica y aguda, enfermedades oseas y afecciones oculares con proliferación vascular retiniana, en un animal de sangre caliente tal como el hombre

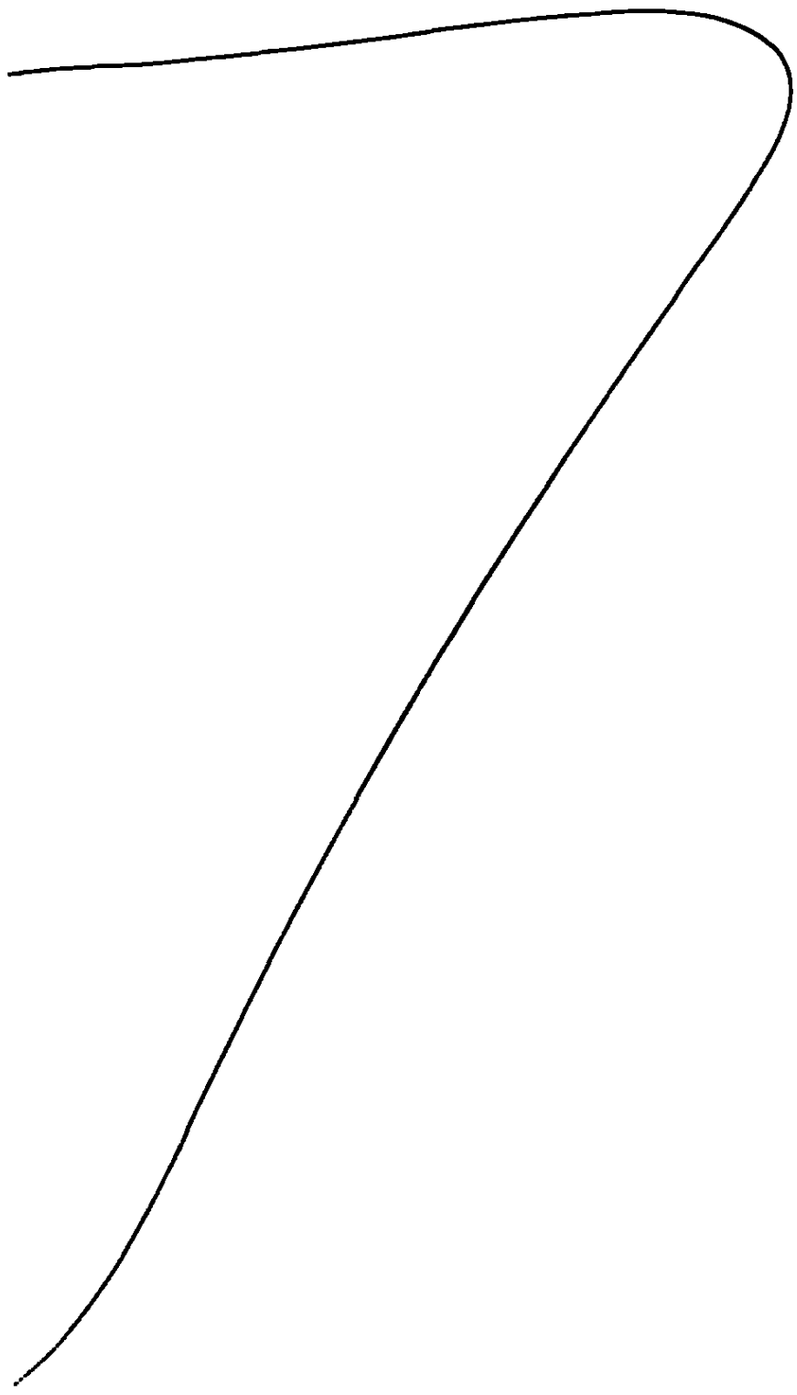
28 Una composicion farmaceutica que comprende un compuesto de la formula (I), o su sal farmaceuticamente aceptable o ester hidrolizable *in vivo*, como se reivindica en una cualquiera de las reivindicaciones 1-11, en asociacion con un diluyente o vehiculo farmaceuticamente aceptable para uso en el tratamiento de cáncer en un animal de sangre caliente tal como el hombre

29 Una composición farmacéutica como se reivindica en la reivindicación 28 en donde dicho cáncer es leucemia, cancer de mama, cancer de pulmon, cancer de colon, cancer rectal, cáncer del estomago, cancer de próstata, cáncer de vejiga, cancer del páncreas, cáncer de ovarios, cáncer del higado, cáncer del riñon, cáncer de piel y cáncer de la vulva

30 Una composicion farmaceutica que comprende un compuesto de la fórmula (I), o su sal farmacéuticamente aceptable o éster hidrolizable *in vivo*, como se reivindica en una cualquiera de las reivindicaciones 1-11, en asociacion con un diluyente o vehiculo farmaceuticamente aceptable para

294 295

uso en la produccion de un efecto inhibidor de CDK en un animal de sangre caliente tal como el hombre



INTERNATIONAL SEARCH REPORT

Inte val Application No
PCT/GB2005/000303

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/04 C07D403/14

294 & 296

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

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/066480 A (ASTRAZENECA AB, BERG, STEFAN, BHAT, RATAN, HELLBERG, SVEN) 29 August 2002 (2002-08-29) page 1, paragraph 1 page 5, paragraph 1 page 5, Formula (I) page 43, Example 99	1-30
A	WO 02/20512 A (ASTRAZENECA AB, ASTRAZENECA UK LIMITED, BREAULT, GLORIA, ANNE, NEWCOMB) 14 March 2002 (2002-03-14) cited in the application page 1, paragraph 1 page 2, Formula (I) page 29, paragraph 3 Examples 26, 77, 79	1-30

☐ 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
11 May 2005	23/05/2005

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	Hoepfner, W

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

ational application No
PCT/GB2005/000303

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

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

Although claims 21-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition

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

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

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

Inte ial Application No
PC1/GB2005/000303

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02066480 A	29-08-2002	BR 0207096 A	20-01-2004
		CA 2435177 A1	29-08-2002
		EP 1423388 A2	02-06-2004
		JP 2004522777 T	29-07-2004
		MX PA03007266 A	04-12-2003
		NO 20033677 A	02-10-2003
		WO 02066480 A2	29-08-2002
		US 2004106574 A1	03-06-2004
WO 0220512 A	14-03-2002	AT 269327 T	15-07-2004
		AU 8419201 A	22-03-2002
		BG 107579 A	31-10-2003
		BR 0113496 A	01-07-2003
		CA 2417148 A1	14-03-2002
		CN 1452620 A	29-10-2003
		CZ 20030617 A3	18-06-2003
		DE 60103935 D1	22-07-2004
		DK 1351958 T3	06-09-2004
		EE 200300088 A	15-02-2005
		EP 1351958 A1	15-10-2003
		WO 0220512 A1	14-03-2002
		HK 1057553 A1	31-12-2004
		HU 0302922 A2	29-12-2003
		JP 3523641 B2	26-04-2004
		JP 2004508365 T	18-03-2004
		MX PA03001511 A	09-06-2003
		NO 20031006 A	04-03-2003
		NZ 523787 A	24-09-2004
		PL 360627 A1	20-09-2004
		PT 1351958 T	30-09-2004
		SI 1351958 T1	31-10-2004
		SK 2412003 A3	11-09-2003
		US 2004014776 A1	22-01-2004
		ZA 200300612 A	22-04-2004

30+ 299

PCT REQUEST

Original (for SUBMISSION)

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-SAFE [EASY mode] Version 3 50 (Build 0002 163)
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	101370-1 WO
I	Title of invention	CHEMICAL COMPOUNDS
II	Applicant	
II-1	This person is	applicant only
II-2	Applicant for	AP: (BW GH GM KE LS MW MZ NA 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 PL 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 BW 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 NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
II-4	Name	ASTRAZENECA AB
II-5	Address	SE-151 85 Sodertalje Sweden
II-6	State of nationality	SE
II-7	State of residence	SE
II-8	Telephone No	+44 1625 230148
II-9	Facsimile No	+46 8553 28820

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)	ANDREWS David, Michael
III-2-5	Address	AstraZeneca R&D Alderley Alderley Park Macclesfield Cheshire SK10 4TG United Kingdom
III-2-6	State of nationality	GB
III-2-7	State of residence	GB
III-3	Applicant and/or inventor	
III-3-1	This person is	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST First)	FINLAY Maurice, Raymond, Verschoyle
III-3-5	Address	AstraZeneca R&D Alderley Alderley Park Macclesfield Cheshire SK10 4TG United Kingdom
III-3-6	State of nationality	GB
III-3-7	State of residence	GB

III-4	Applicant and/or inventor	
III-4-1	This person is	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST First)	GREEN, Clive
III-4-5	Address	AstraZeneca R&D Alderley Alderley Park Macclesfield Cheshire SK10 4TG United Kingdom
III-4-6	State of nationality	GB
III-4-7	State of residence	GB
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	ASTRAZENECA
IV-1-2	Address	Global Intellectual Property SE-151 85 Sodertalje Sweden
IV-1-3	Telephone No.	+44 1625 230148
IV-1-4	Facsimile No.	+46 8553 28820
V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	03 February 2004 (03 02 2004)
VI-1-2	Number	0402277 8
VI-1-3	Country	GB
VI-2	Priority claim of earlier national application	
VI-2-1	Filing date	28 May 2004 (28 05 2004)
VI-2-2	Number	0411998 8
VI-2-3	Country	GB
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)

304 302

PCT REQUEST

Original (for SUBMISSION)

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	118	-
IX-3	Claims	12	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	136	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX 11	Copy of general power of attorney	reference no AZAB/AUG04/003	-
IX-11	Copy of general power of attorney	reference no AZUK/AUG04/003	-
IX 13	Priority document(s)	Item(s) VI-1 VI-2	-
IX 17	PCT-SAFE physical media	-	✓
IX-18	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	ASTRAZENECA	
X-1 2	Name of signatory	GAINEY Laurence David Scott	
X 1 3	Capacity	Agent	

AS 101675

101370-1P CO

ASSIGNMENT

The undersigned,

ANDREWS, David, Michael FINLAY Maurice Raymond and GREEN Clive

domiciled in
AstraZeneca R&D Alderley Alderley Park,
Macclesfield Cheshire SK10 4TG United Kingdom

hereby state under oath to be the sole and true inventor of

IMIDAZOLO-5 YL-2 ANILINOPYRIMIDINES AS AGENTS FOR THE INHIBITION OF CELL PROLIFERATION

state as well that 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 Södertälje, 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

ANDREWS David, Michael

GREEN Clive

TRASPASO

abajo firmado

2

304

306

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 leves 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

FINLAY Maurice, Raymond

Presented before me at
35 Windsor Road Slough
Berkshire
This 12th day of July 2006
George Andrew Lewis
Notary Public

271949

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

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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 présent acte public*

2. Has been signed by: **George Andrew Lewis**
a été 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* **13 July 2006**

7 by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/*sous No* **H077168**

9. Stamp:
timbre:

10. Signature: **N Donker**

FOREIGN AND COMMONWEALTH OFFICE LONDON

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. 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.

7 of 306

TRADUCCION AL ESPAÑOL del Documento de Cesión a **AstraZeneca AB** firmado por los cedentes y el cesionario

---

En el documento de cesión hay un sello que dice

Presentado ante mi en
35 Windsor Road Slough
Berkshire
Este 12 de julio de 2006-08-10 Goerge Andrew Lewis
Notario Público

Al respaldo del documento de cesión hay un anexo que dice

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 firmad por **George Andrew Lewis**

3 actuando en capacidad de **Notario público**

4 lleva el sello/timbre de **dicho notario público**

Certificado

5 en Londres 6 **el 13 de julio de 2006**

7 por el Secretario de estado Principal de Su Majestad para Relaciones Exteriores y de la Mancomunidad

8 No **H077168**

9 Sello 10 Firma **N Donkor**

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 ante la sección consular de la misión que representa a ese país Una apostilla o certificado de legalización solo confirma que la firma sello o timbre en el documento son genuinos No significa que los contenidos del documento estén correctos o que la Oficina de Extranjería y de la Mancomunidad pruebe los contenidos

Brigard & Castro

BOGOTA COLOMBIA

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 egistrar 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 creyeran 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 y 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, [illegible] (our) attorney(s) in fact with powers to receive notifications and to designate judicial and extrajudicial attorneys

Granted and signed in [illegible] on [illegible]

this 18th day

Signature

Name KEVIN BILL
Title Director IP Services

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)

CERTIFICADO NOTARIAL PERSONA NATURAL

Hoy de de compareció(aron) 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)

LEGALIZACION POR APOSTILLA ES REQUERIDA

NOTARIAL CERTIFICATE (CORPORATION)

On this 18th day of July 2003 of
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)

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

06 MAR 2003
OSCAR A. ARROCHA NUÑEZ
NOTARIO CIRCUITO Y SELLO

Notary Public (Seal)

LEGALIZATION BY APOSTILLE IS REQUIRED

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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 présent acte public

2. Has been signed by J B Hodgson
a été 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 Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **G348987**

9. Stamp:
timbre:

10. Signature: J. Ireland

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

COMO NOTARIO CERTIFICO Y DOY FE DE LA EXACTITUD DE LA FOTOCOPIA QUE PRECEDE, QUE HE TENIDO A LA VISTA

06 MAR 2009

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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**

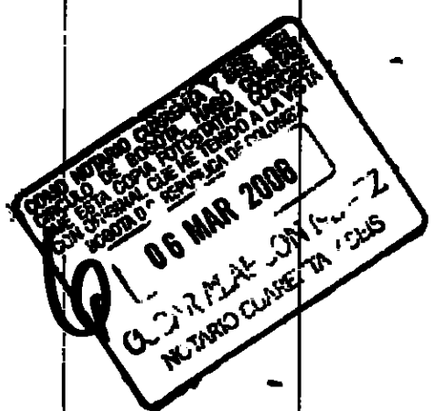
7 por El secretario de Estado Principal de Su Majestad para Asuntos Exteriores y de la Comunidad

8 No **G348987**

9 Sello 10 Firma

J Ireland (Firma)

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



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad 06-076881--00000-0000
Fec 2006-08-10 17:00:04 Dep 2020 NUECREACIONES
Tra 11 PATENTES(I)
Cla 370 FASENACIONAL)
Act 411 PRESENTACION Folios 310

Industria y Comercio
SUPERINTENDENCIA

311
310

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesion de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción 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 gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha 10-Ag-06

Carrera 13 No 27 00 Piso 5 7 y 10
Conmutador 3 82 08 40
Fax 350 52 20
E mail info@sic gov co
www sic gov co
Bogotá D C Colombia

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

311

Folio 312

2020
Bogotá D C

Doctor(a)
CADENA SARMIENTO JUAN PABLO
Apoderado(a) y/o Representante de
ASTRAZENECA AB

REFERENCIA	Radicación No	06 78881
	Solicitud internacional	GB2005/000303
	Fecha inicio fase nacional	03/09/2006
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No	1434
	Folios	1

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 29 SET 2006

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

adpa1