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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Act. 411 PRESENTACION Folios: 152**FORMULARIO ÚNICO DE SOLICITUD DE PATENTE**
PCT
ENTRADA EN FASE NACIONAL

1

SOLICITUD DE:☒ Patente de Invención.☐ Patente de Modelo de Utilidad.☒ Capítulo I.☐ Capítulo II.

2

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3

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Número 80.410.337 TP 57492

4

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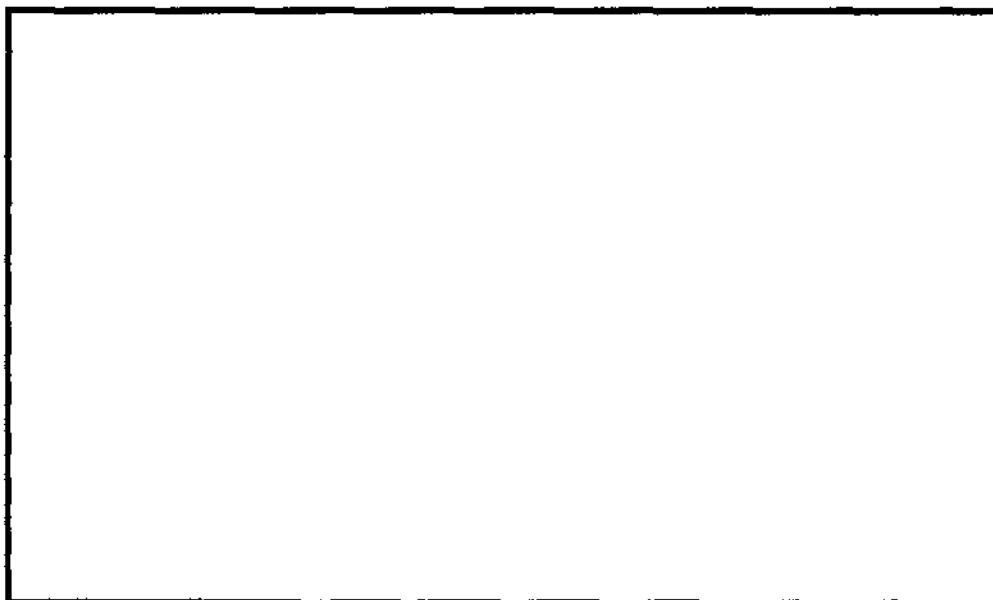
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

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ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$ 501.000
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. **Fotocopia autenticada**
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: Tarjeta de Propietarios
Documentos PCT

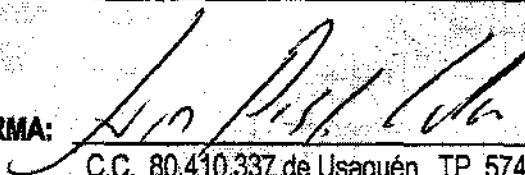
11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente,

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA:



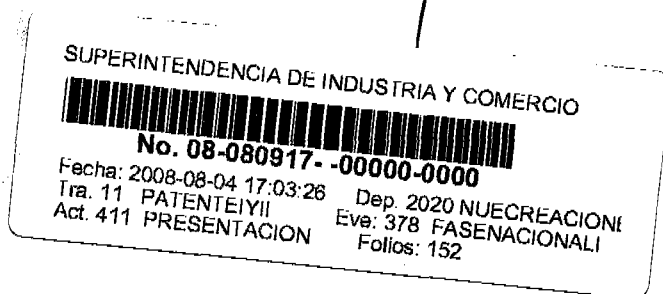
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	501,000.00
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4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

PATENTE ☒ PCT/GB2007/000310 MODELO DE UTILIDAD ☐ DISEÑO INDUSTRIAL ☐

SOLICITANTE/S. RAZON SOCIAL O APELLIDOS Y NOMBRES UCB PHARMA, S.A.

DOMICILIO BRUSELAS, BELGICA

APODERADO JUAN PABLO CADENA SARMIENTO

TITULO DERIVADOS DE TIENO-PIRIDINA. COMO INHIBIDORES DE MEK

CLASIFICACION

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VIGENCIA DESDE

HASTA

PRORROGA

CAMBIO DE NOMBRE

TRASPASO A

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(54) Title: THIENO-PYRIDINE DERIVATIVES AS MEK INHIBITORS

(57) Abstract: A series of thieno[2,3-*b*]pyridine derivatives which are substituted in the 2- position by a substituted anilino moiety, being selective inhibitors of human MEK (MAPKK) enzymes, are accordingly of benefit in medicine, for example in the treatment of inflammatory, autoimmune, cardiovascular, proliferative (including oncological) and nociceptive conditions.

WO 2007/088345 A1

THIENO-PYRIDINE DERIVATIVES AS MEK INHIBITORS

The present invention relates to a class of thieno-pyridine derivatives and to their use in therapy. More particularly, the invention is concerned with thieno[2,3-*b*]pyridine derivatives which are substituted in the 2-position by a substituted anilino moiety. These compounds are selective inhibitors of MEK (MAPKK) enzymes, and are accordingly of benefit as pharmaceutical agents, especially in the treatment of adverse inflammatory, autoimmune, cardiovascular, proliferative (including oncological) and nociceptive conditions.

MEK enzymes are implicated in a variety of physiological and pathological functions that are believed to be operative in a range of human diseases. These functions are summarised in paragraphs [0004] and [0005] of US 2005/0049276 A1.

The compounds of use in the present invention, being potent and selective MEK inhibitors, are therefore beneficial in the treatment and/or prevention of various human ailments. These include autoimmune and inflammatory disorders such as rheumatoid arthritis, osteoarthritis, multiple sclerosis, asthma, inflammatory bowel disease, psoriasis and transplant rejection; cardiovascular disorders including thrombosis, cardiac hypertrophy, hypertension, and irregular contractility of the heart (e.g. during heart failure); proliferative disorders such as restenosis, and oncological conditions including leukaemia, glioblastoma, lymphoma, melanoma, and human cancers of the liver, bone, skin, brain, pancreas, lung, breast, stomach, colon, rectum, prostate, ovary and cervix; and pain and nociceptive disorders, including chronic pain and neuropathic pain.

In addition, the compounds of use in the present invention may be beneficial as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents. Thus, the compounds of use in this invention may be useful as radioligands in assays for detecting compounds capable of binding to human MEK enzymes.

MEK inhibitors based on a fused bicyclic aromatic ring system attached to a substituted anilino moiety are known from the art. Examples of relevant publications include WO 2005/051906, WO 2005/023251, US-A-2005/0049276, WO 2005/009975, WO 03/077914 and WO 03/077855.

WO 2005/023818 describes a broad-ranging class of compounds based on a fused bicyclic aromatic ring system, which generically encompasses thieno-pyridine derivatives

attached to a substituted anilino moiety but nowhere specifically discloses any precise compound of this type. No discrete pharmacological activity, in terms of an identifiable pharmacological mechanism, is ascribed to the compounds described therein, but they are nevertheless stated to be useful *inter alia* in the treatment of cell proliferative diseases

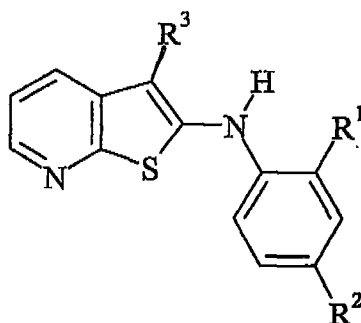
5 such as cancer. US-A-2003/0220365 is also of relevance in a related context.

Nowhere in the prior art, however, is there the precise disclosure of a class of thieno[2,3-*b*]pyridine derivatives attached at the 2-position to a substituted anilino moiety. It has now been found that such compounds are particularly valuable as selective inhibitors of MEK enzymes.

- 10 The compounds of the present invention are potent and selective MEK inhibitors having a binding affinity (IC_{50}) for the human MEK1 and/or MEK2 enzyme of 50 μ M or less, generally of 20 μ M or less, usually of 5 μ M or less, typically of 1 μ M or less, suitably of 500 nM or less, ideally of 100 nM or less, and preferably of 20 nM or less (the skilled person will appreciate that a *lower* IC_{50} figure denotes a *more active* compound).
- 15 The compounds of the invention may possess at least a 10-fold selective affinity, typically at least a 20-fold selective affinity, suitably at least a 50-fold selective affinity, and ideally at least a 100-fold selective affinity, for the human MEK1 and/or MEK2 enzyme relative to other human kinases.

The present invention provides a compound of formula (I), or a pharmaceutically

20 acceptable salt, solvate or *N*-oxide thereof:



(I)

wherein

- 25 R^1 represents hydrogen, halogen or C_{1-6} alkyl;
 R^2 represents halogen or C_{1-6} alkyl;
 R^3 represents hydrogen, cyano, $-CO_2R^a$, $-CONR^bR^c$ or $-CON(OR^b)R^c$;

R^a represents C₁₋₆ alkyl;

R^b represents hydrogen; or C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents; and

R^c represents hydrogen or C₁₋₆ alkyl (optionally substituted by hydroxy); or

R^b and R^c, when taken together with the nitrogen atom to which they are both attached, represent azetidiny, pyrrolidiny, piperidiny, morpholiny, thiomorpholiny, piperaziny, homopiperidiny, homomorpholiny or homopiperaziny, any of which groups may be optionally substituted by one or more substituents.

The present invention also provides a compound of formula (I) as depicted above, or a pharmaceutically acceptable salt, solvate or *N*-oxide thereof, wherein

R¹ and R² are as defined above;

R³ represents cyano, -CO₂R^a, -CONR^bR^c or -CON(OR^b)R^c;

R^a represents C₁₋₆ alkyl;

R^b represents hydrogen; or C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents; and

R^c represents hydrogen or C₁₋₆ alkyl; or

R^b and R^c, when taken together with the nitrogen atom to which they are both attached, represent azetidiny, pyrrolidiny, piperidiny, morpholiny, thiomorpholiny, piperaziny, homopiperidiny or homomorpholiny, any of which groups may be optionally substituted by one or more substituents.

For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound of the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, e.g. carboxy,

suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The present invention includes within its scope solvates of the compounds of formula (I) above. Such solvates may be formed with common organic solvents, e.g. hydrocarbon solvents such as benzene or toluene; chlorinated solvents such as chloroform or dichloromethane; alcoholic solvents such as methanol, ethanol or isopropanol; ethereal solvents such as diethyl ether or tetrahydrofuran; or ester solvents such as ethyl acetate. Alternatively, the solvates of the compounds of formula (I) may be formed with water, in which case they will be hydrates.

Suitable alkyl groups which may be present on the compounds of the invention include straight-chained and branched C₁₋₆ alkyl groups, for example C₁₋₄ alkyl groups. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl, butyl and pentyl groups. Particular alkyl groups include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl and 2,2-dimethylpropyl. Derived expressions such as "C₁₋₆ alkoxy", "C₁₋₆ alkylthio", "C₁₋₆ alkylsulphonyl" and "C₁₋₆ alkylamino" are to be construed accordingly.

Specific C₃₋₇ cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Suitable aryl groups include phenyl and naphthyl, preferably phenyl.

Suitable aryl(C₁₋₆)alkyl groups include benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

Suitable heterocycloalkyl groups, which may comprise benzo-fused analogues thereof, include azetidiny, tetrahydrofuranyl, dioxolanyl, pyrrolidinyl, indolinyl, imidazolidinyl, tetrahydropyranyl, piperidinyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, piperazinyl, morpholinyl and thiomorpholinyl.

Suitable heteroaryl groups include furyl, benzofuryl, dibenzofuryl, thienyl, benzothienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl and pyrazinyl groups.

The term "halogen" as used herein is intended to include fluorine, chlorine, bromine and iodine atoms.

Where the compounds of formula (I) have one or more asymmetric centres, they may accordingly exist as enantiomers. Where the compounds of the invention possess two or more asymmetric centres, they may additionally exist as diastereomers. The invention is to be understood to extend to all such enantiomers and diastereomers, and to mixtures thereof in any proportion, including racemates. Formula (I) and the formulae depicted hereinafter are intended to represent all individual stereoisomers and all possible mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (I) may exist as tautomers, for example keto ($\text{CH}_2\text{C}=\text{O}$)-enol ($\text{CH}=\text{CHOH}$) tautomers. Formula (I) and the formulae depicted hereinafter are intended to represent all individual tautomers and all possible mixtures thereof, unless stated or shown otherwise.

In one embodiment, R^1 represents hydrogen. In another embodiment, R^1 represents halogen, particularly fluoro or chloro, especially fluoro. In a further embodiment, R^1 represents C_{1-6} alkyl, especially methyl.

Typically, R^1 is fluoro.

In one embodiment, R^2 represents halogen, especially bromo or iodo. In another embodiment, R^2 represents C_{1-6} alkyl, especially methyl.

In one specific embodiment, R^2 is bromo. In another specific embodiment, R^2 is iodo.

Suitably, R^a represents methyl or ethyl, especially ethyl.

Favourably, R^b represents hydrogen; or C_{1-6} alkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl or C_{3-7} heterocycloalkyl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

Suitably, R^b represents hydrogen; or C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

Suitably, the group R^b , or the cyclic moiety $-\text{NR}^b\text{R}^c$, may be unsubstituted, or substituted by one or more substituents, typically by one or two substituents. In one embodiment, the group R^b , or the cyclic moiety $-\text{NR}^b\text{R}^c$, is unsubstituted. In another embodiment, the group R^b , or the cyclic moiety $-\text{NR}^b\text{R}^c$, is monosubstituted. In a further embodiment, the group R^b , or the cyclic moiety $-\text{NR}^b\text{R}^c$, is disubstituted.

Examples of typical substituents on R^b , or on the cyclic moiety $-\text{NR}^b\text{R}^c$, include C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, hydroxy(C_{1-6})alkyl, amino(C_{1-6})alkyl, (amino)(hydroxy)-(C_{1-6})alkyl, halogen, oxo, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxycarbonyl,

di(C₁₋₆)alkylhydrazinylcarbonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonylamino, aminocarbonylamino, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulfonyl, C₁₋₆ alkylsulfonyl and C₁₋₆ alkylaminocarbonyl(C₁₋₆)alkyl. Further examples include C₁₋₆ alkoxy(C₁₋₆)alkyl, 5 carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonylamino and C₂₋₆ alkoxycarbonylamino(C₁₋₆)alkyl.

Examples of particular substituents on R^b, or on the cyclic moiety -NR^bR^c, include methyl, methoxy, hydroxy, hydroxymethyl, 2-hydroxyethyl, aminomethyl, 2-amino-3-hydroxypropyl, fluoro, oxo, acetyl, carboxy, methoxycarbonyl, ethoxycarbonyl, *tert*-10 butoxycarbonyl, dimethylhydrazinylcarbonyl, amino, methylamino, 1,3-dimethylbutylamino, dimethylamino, acetylamino, aminocarbonylamino, aminocarbonyl, ethylaminocarbonyl, diethylaminocarbonyl, aminosulfonyl, methylsulfonyl and methylaminocarbonylmethyl. Further examples include methoxymethyl, carboxymethyl, ethoxycarbonylmethyl, *tert*-butoxycarbonylamino and *tert*-butoxycarbonylaminomethyl.

15 Examples of favoured substituents on R^b, or on the cyclic moiety -NR^bR^c, include C₁₋₆ alkyl, C₁₋₆ alkoxy(C₁₋₆)alkyl, hydroxy, hydroxy(C₁₋₆)alkyl, amino, amino(C₁₋₆)alkyl, carboxymethyl, C₂₋₆ alkoxycarbonyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, di(C₁₋₆)alkylamino, C₂₋₆ alkoxycarbonylamino and C₂₋₆ alkoxycarbonylamino(C₁₋₆)alkyl.

Examples of specific substituents on R^b, or on the cyclic moiety -NR^bR^c, include 20 methyl, methoxymethyl, hydroxy, hydroxymethyl, 2-hydroxyethyl, amino, aminomethyl, carboxymethyl, *tert*-butoxycarbonyl, ethoxycarbonylmethyl, dimethylamino, *tert*-butoxycarbonylamino and *tert*-butoxycarbonylaminomethyl.

Favoured values of R^b include hydrogen, methyl, ethyl, propyl, cyclopropylmethyl, azetidiny, pyrrolidinyl, piperidinyl, azetidinylmethyl, dioxolanylmethyl, 25 pyrrolidinylmethyl, morpholinylethyl and morpholinylpropyl, any of which groups may be optionally substituted by one or more substituents. Favoured substituents in this context include C₁₋₆ alkyl (especially methyl), hydroxy, amino, C₂₋₆ alkoxycarbonyl (especially *tert*-butoxycarbonyl) and di(C₁₋₆)alkylamino (especially dimethylamino).

Specific values of R^b include hydrogen, methyl, 2-hydroxyethyl, 3-hydroxypropyl, 30 1-hydroxyprop-2-yl, 2,3-dihydroxypropyl, 2-amino-2-methylpropyl, 2,2-dimethyl-3-(dimethylamino)propyl, cyclopropylmethyl, 1-*tert*-butoxycarbonylazetid-3-yl, pyrrolidin-3-yl, 1-*tert*-butoxycarbonylpyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, 1-methylpiperidin-4-yl, 1-*tert*-butoxycarbonylpiperidin-3-yl, 1-*tert*-butoxycarbonyl-

piperidin-4-yl, 1-*tert*-butoxycarbonylazetidin-3-ylmethyl, 2,2-dimethyl-[1,3]dioxolan-4-ylmethyl, pyrrolidin-2-ylmethyl, 2-(morpholin-4-yl)ethyl and 3-(morpholin-4-yl)propyl.

Typically, R^b represents hydrogen; or C_{1-6} alkyl, optionally substituted by one or more, preferably one or two, hydroxy groups.

5 Typical values of R^b include hydrogen, methyl, hydroxypropyl and dihydroxypropyl. In one embodiment, R^b represents hydrogen. In another embodiment, R^b represents methyl. In a further embodiment, R^b represents hydroxypropyl, especially 3-hydroxypropyl. In an additional embodiment, R^b represents dihydroxypropyl, especially 2,3-dihydroxypropyl.

10 In one embodiment, R^c is hydrogen. In another embodiment, R^c represents C_{1-6} alkyl, especially methyl. In a further embodiment, R^c represents hydroxy(C_{1-6})alkyl, e.g. hydroxyethyl (especially 2-hydroxyethyl).

Alternatively, the moiety $-NR^bR^c$ may suitably represent azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperazin-1-yl, homopiperidin-1-yl or homomorpholin-4-yl, any of which groups may be optionally substituted by one or
15 more substituents. The moiety $-NR^bR^c$ may also represent optionally substituted homopiperazin-1-yl.

Particular values for the cyclic moiety $-NR^bR^c$ include azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl and homopiperazin-1-yl, any of which
20 groups may be optionally substituted by one or more substituents.

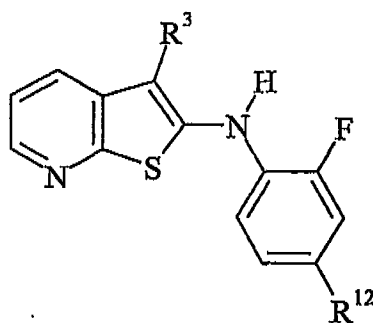
Specific values of the cyclic moiety $-NR^bR^c$ include 3-hydroxyazetidin-1-yl, 3-aminoazetidin-1-yl, 3-(aminomethyl)azetidin-1-yl, 3-(*tert*-butoxycarbonylamino)azetidin-1-yl, 3-(*tert*-butoxycarbonylaminomethyl)azetidin-1-yl, pyrrolidin-1-yl, 2-(methoxymethyl)pyrrolidin-1-yl, 3-hydroxypyrrolidin-1-yl, 3-aminopyrrolidin-1-yl, 3-(*tert*-
25 butoxycarbonylamino)pyrrolidin-1-yl, 2-(hydroxymethyl)piperidin-1-yl, 4-amino-piperidin-1-yl, 4-(*tert*-butoxycarbonylamino)piperidin-1-yl, morpholin-4-yl, 2-(hydroxymethyl)morpholin-4-yl, piperazin-1-yl, 4-methylpiperazin-1-yl, 2-(hydroxymethyl)-piperazin-1-yl, 4-(2-hydroxyethyl)piperazin-1-yl, 4-(carboxymethyl)piperazin-1-yl, 4-(*tert*-butoxycarbonyl)-2-(hydroxymethyl)piperazin-1-yl, 4-(ethoxycarbonylmethyl)-
30 piperazin-1-yl and homopiperazin-1-yl.

Suitably, the cyclic moiety $-NR^bR^c$ may be substituted by C_{1-6} alkyl, especially methyl. Particular values of $-NR^bR^c$ include pyrrolidin-1-yl, morpholin-4-yl and 4-methylpiperazin-1-yl.

Typically, R^3 represents cyano, $-CO_2R^a$, $-CONR^bR^c$, or $-CON(OR^b)R^c$, in which R^a , R^b and R^c are as defined above. Suitably, R^3 represents cyano, $-CO_2R^a$ or $-CONR^bR^c$, especially cyano or $-CONR^bR^c$, in which R^a , R^b and R^c are as defined above. Suitably, R^3 represents $-CON(OR^b)R^c$, in which R^b and R^c are as defined above.

5 In one embodiment, R^3 represents cyano. In another embodiment, R^3 represents $-CO_2R^a$, in which R^a is as defined above. In a further embodiment, R^3 represents $-CONR^bR^c$, in which R^b and R^c are as defined above. In an additional embodiment, R^3 represents $-CON(OR^b)R^c$, in which R^b and R^c are as defined above. In a still further embodiment, R^3 represents hydrogen.

10 A particular sub-group of compounds according to the invention is represented by the compounds of formula (II), and pharmaceutically acceptable salts, solvates and *N*-oxides thereof:



(II)

15

wherein

R^{12} represents halogen; and

R^3 is as defined above.

In one specific embodiment, R^{12} is bromo. In another specific embodiment, R^{12} is
20 iodo.

Specific novel compounds in accordance with the present invention include each of the compounds whose preparation is described in the accompanying Examples, and pharmaceutically acceptable salts and solvates thereof.

25 The present invention also provides a pharmaceutical composition which comprises a compound of formula (I) as defined above, or a pharmaceutically acceptable salt, solvate or *N*-oxide thereof, in association with one or more pharmaceutically acceptable carriers.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical, ophthalmic or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, 5 for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methyl cellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogenphosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting 10 agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as 15 suspending agents, emulsifying agents, non-aqueous vehicles or preservatives. The preparations may also contain buffer salts, flavouring agents, colouring agents or sweetening agents, as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

20 For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of formula (I) may be formulated for parenteral administration by injection, e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoules or multi-dose containers, e.g. glass vials. The 25 compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

30 In addition to the formulations described above, the compounds of formula (I) may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds according to the present invention may be conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, fluorotrichloromethane, dichlorotetrafluoroethane, carbon
5 dioxide or other suitable gas or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

For topical administration the compounds according to the present invention may
10 be conveniently formulated in a suitable ointment containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, liquid petroleum, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax and water. Alternatively, the compounds according to the present invention may be formulated in a suitable lotion
15 containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, benzyl alcohol, 2-octyldodecanol and water.

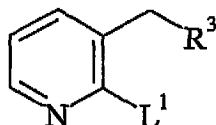
For ophthalmic administration the compounds according to the present invention
20 may be conveniently formulated as microionized suspensions in isotonic, pH-adjusted sterile saline, either with or without a preservative such as a bactericidal or fungicidal agent, for example phenylmercuric nitrate, benzylalkonium chloride or chlorhexidine acetate. Alternatively, for ophthalmic administration compounds may be formulated in an ointment such as petrolatum.

25 For rectal administration the compounds according to the present invention may be conveniently formulated as suppositories. These can be prepared by mixing the active component with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and so will melt in the rectum to release the active component. Such materials include, for example, cocoa butter, beeswax and polyethylene glycols.

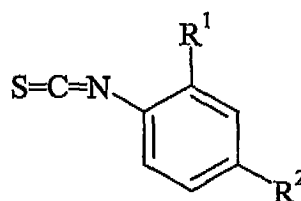
30 The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen and the condition of the patient to be treated. In general, however, daily dosages may range from around 10 ng/kg to 1000 mg/kg, typically from 100 ng/kg to 100 mg/kg, e.g. around 0.01

mg/kg to 40 mg/kg body weight, for oral or buccal administration, from around 10 ng/kg to 50 mg/kg body weight for parenteral administration, and from around 0.05 mg to around 1000 mg, e.g. from around 0.5 mg to around 1000 mg, for nasal administration or administration by inhalation or insufflation.

- 5 The compounds of formula (I) above, and the *N*-oxides thereof, may be prepared by a process which comprises reacting a compound of formula (III), or an *N*-oxide thereof, with a compound of formula (IV):



(III)



(IV)

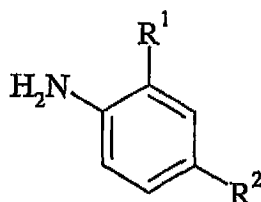
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wherein R^1 , R^2 and R^3 are as defined above, and L^1 represents a suitable leaving group.

The leaving group L^1 is typically a halogen atom, e.g. chloro.

- The reaction is conveniently effected, at an elevated temperature if necessary, in a suitable solvent, e.g. dimethylsulphoxide, typically under basic conditions, e.g. in the
15 presence of an inorganic base such as sodium hydride.

The intermediates of formula (IV) above may be prepared by reacting a compound of formula (V):



(V)

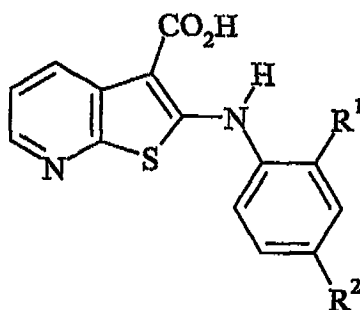
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wherein R^1 and R^2 are as defined above; with thiophosgene.

The reaction is conveniently effected in a suitable solvent, typically a mixture of chloroform and water.

In another procedure, the compounds of formula (I) above wherein R^3 represents $-\text{CONR}^b\text{R}^c$ or $-\text{CON}(\text{OR}^b)\text{R}^c$, and the *N*-oxides thereof, may be prepared by a process which comprises reacting a compound of formula $\text{H-NR}^b\text{R}^c$ or $\text{H-N}(\text{OR}^b)\text{R}^c$ with a compound of formula (VI), or an *N*-oxide thereof:

5

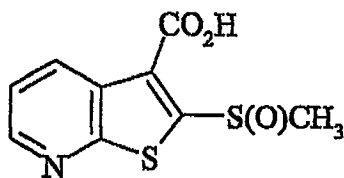


(VI)

wherein R^1 , R^2 , R^b and R^c are as defined above; in the presence of a condensing agent.

A suitable condensing agent is 1-(3-dimethylaminopropyl)-3-carbodiimide hydrochloride (EDC), in which case the reaction is conveniently effected in the presence of 1-hydroxybenzotriazole (HOBT) and *N*-methylmorpholine (NMM).

The compounds of formula (VI) above may be prepared by reacting the compound of formula (VII):



(VII)

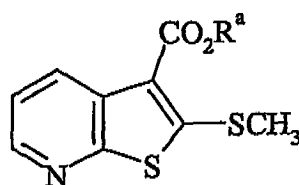
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with a compound of formula (V) as defined above.

The reaction may conveniently be effected by treating compound (V) with a base, e.g. lithium bis(trimethylsilyl)amide, in a suitable solvent, e.g. tetrahydrofuran, followed by the addition of compound (VII).

20

The intermediate of formula (VII) above may be prepared from a compound of formula (VIII):



(VIII)

wherein R^a is as defined above; by saponification of the ester moiety followed by
5 oxidation of the methylsulfanyl group.

Saponification of the ester moiety $-CO_2R^a$ in compound (VIII) may be effected by treatment with an alkaline base, e.g. sodium hydroxide, in a suitable solvent, e.g. an aqueous mixture of a lower alkanol such as methanol and a cyclic ether such as tetrahydrofuran. Oxidation of the methylsulfanyl group in the resulting compound may
10 then be effected by treatment with a suitable oxidising agent, e.g. Oxone® (potassium peroxymonosulfate), in an appropriate solvent, e.g. aqueous methanol.

The intermediates of formula (VIII) above may be prepared by reacting a compound of formula (III), wherein R^3 is $-CO_2R^a$ as defined above, with carbon disulfide, followed by treatment with a methyl halide such as iodomethane.

15 The reaction is conveniently effected in a suitable solvent, e.g. dimethylsulfoxide, in the presence of a base such as sodium hydride.

Where they are not commercially available, the starting materials of formula (III) and (V) may be prepared by methods analogous to those described in the accompanying Examples, or by standard methods well known from the art.

20 It will be understood that any compound of formula (I) initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula (I) by techniques known from the art. By way of example, a compound of formula (I) wherein R^3 represents $-CO_2R^a$ may be converted into the corresponding compound wherein R^3 represents $-CONH_2$ by treatment with ammonia, typically in a lower alkanol solvent, e.g. ethanol, at elevated temperature and pressure.
25 Alternatively, a compound of formula (I) wherein R^3 represents $-CO_2R^a$ may be converted into the corresponding compound wherein R^3 represents $-CONR^bR^c$ by treatment with the appropriate amine of formula $H-NR^bR^c$ in the presence of trimethylaluminium. A compound of formula (I) wherein R^3 represents $-CO_2R^a$ may be converted into the

- corresponding compound wherein R^3 represents hydrogen by treatment with an alkaline reagent such as lithium hydroxide under forcing conditions, e.g. by heating at reflux in a mixture of ethanol and water. A compound of formula (I) wherein R^3 contains a 2,2-dimethyl-[1,3]dioxolan-4-ylmethyl moiety may be converted into the corresponding
- 5 compound wherein R^3 contains a 2,3-dihydroxypropyl moiety by treatment with a mineral acid such as hydrochloric acid. A compound of formula (I) wherein R^3 contains a nitrogen atom to which a *tert*-butoxycarbonyl (BOC) group is attached may be converted into the corresponding compound wherein R^3 contains an N-H functionality by treatment with an acid, e.g. a mineral acid such as hydrochloric acid, or an organic acid such as
- 10 trifluoroacetic acid. A compound of formula (I) wherein R^3 contains an N-H functionality may be converted into the corresponding compound wherein R^3 contains a nitrogen atom to which an ethoxycarbonylmethyl group is attached by treatment with ethyl chloroacetate, typically in the presence of triethylamine; the resulting compound may then be converted into the corresponding compound wherein R^3 contains a nitrogen
- 15 atom to which a carboxymethyl group is attached by treatment with an alkaline reagent such as sodium hydroxide, typically in an aqueous solution of a lower alkanol such as ethanol. The pyridine-*N*-oxide derivative of a compound of formula (I) may be converted into the corresponding compound of formula (I) by treatment with triphenyl phosphine and phosphorus trichloride.
- 20 Where a mixture of products is obtained from any of the processes described above for the preparation of compounds according to the invention, the desired product can be separated therefrom at an appropriate stage by conventional methods such as preparative HPLC; or column chromatography utilising, for example, silica and/or alumina in conjunction with an appropriate solvent system.
- 25 Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques. In particular, where it is desired to obtain a particular enantiomer of a compound of formula (I) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for
- 30 resolving enantiomers. Thus, for example, diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (I), e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation, and the desired enantiomer

recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt. In another resolution process a racemate of formula (I) may be separated using chiral HPLC. Moreover, if desired, a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above. Alternatively, a particular enantiomer may be obtained by performing an enantiomer-specific enzymatic biotransformation, e.g. an ester hydrolysis using an esterase, and then purifying only the enantiomerically pure hydrolysed acid from the unreacted ester antipode.

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 3rd edition, 1999. The protecting groups may be removed at any convenient subsequent stage utilising methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds in accordance with this invention potentially inhibit the activity of human MEK enzyme.

In vitro MEK assay

MEK1 activity was measured in a cascade assay initiated by active Raf, via activation of MEK, Erk2 and subsequent phosphorylation of fluorescein-labelled Erk-tide substrate in an assay based on fluorescence polarisation (IMAP). The assay was carried out in 20mM Tris + 5mM MgCl₂ + 2mM DL-dithiothreitol + 0.01% Tween 20 pH 7.2, containing 1.5nM unactive MEK, 100nM unactive Erk and 200nM Erk-tide (all concentrations are final concentrations). Compounds, or DMSO controls, were tested at a final concentration of 2% DMSO, and the assay initiated in the presence of 5μM ATP by addition of 1.25nM active Raf in assay buffer. After 20 min at r.t., stop solution was added followed by IMAP binding beads, the assay mixture was then incubated for 90 min at r.t. (with shaking) and then read on a Molecular Devices LJM HT reader.

When tested in the above assay, the compounds of the accompanying Examples were all found to inhibit human MEK enzyme with IC₅₀ values of 10 µM or better.

EXAMPLES

5

Abbreviations used

EtOAc - ethyl acetate	DMSO - dimethylsulphoxide
THF - tetrahydrofuran	DCM - dichloromethane
ether - diethyl ether	CDCl ₃ - deuteriochloroform
10 MeOH - methanol	MeCN - acetonitrile
EtOH - ethanol	ES - electrospray
DMF - <i>N,N</i> -dimethylformamide	HOBT - 1-hydroxybenzotriazole
SiO ₂ - silica	NMM - <i>N</i> -methylmorpholine
h - hour(s)	min - minute(s)
15 r.t. - room temperature	aq - aqueous
sat. - saturated	RT - retention time
BOC - <i>tert</i> -butoxycarbonyl	LiHMDS - lithium bis(trimethylsilyl)amide
MCPBA - 3-chloroperoxybenzoic acid	
EDC - 1-(3-dimethylaminopropyl)-3-carbodiimide hydrochloride	

20

All NMR spectra were obtained either at 300 MHz or 400 MHz.

Compounds were named with the aid of ACD Labs Name (v. 7.0) supplied by Advanced Chemical Development, Toronto, Canada.

25 *Standard LCMS method*

The LC-MS system used comprises a Waters Alliance 2795 HT quaternary HPLC, Waters 996 Photo Diode Array (PDA) detector and Waters ZQ 4000 single quadrupole mass spectrometer. The ZQ can acquire data simultaneously in positive and negative electrospray ionisation modes.

30

ZQ Mass Spectrometer

Capillary	3.5kV	Cone	50V
Extractor	2V	Source Temp	80°C

Desolvation Temp	200°C	Cone Gas	150 L/h
Desolvation Gas	250 L/h	Multiplier	650V

Data were acquired in a full scan from 100 to 1000 m/z.

Scan duration	0.80 s
5 Interscan delay	0.20 s

HPLC

Analytical reverse phase separation was carried out on a Gemini C18 from Phenomenex 50 x 4.6 mm with 5 µm silica.

10

Injection Volume	5 µL
UV data	240 to 400 nm
Sample Temperature	20°C
Column Temperature	30°C

15

Flow Rate	0.9 mL/min
Split to ZQ	~0.40 mL/min

Solvent A: 90% 10mM NH₄CO₂ in water / 0.1% formic acid / 10% CH₃CN

Solvent B: 90% CH₃CN / 0.1% formic acid / 10% 10mM NH₄CO₂ in water

20

Solvent C: 90% 10mM NH₄CO₂ in water / 0.1% ammonia / 10% CH₃CN

Solvent D: 90% CH₃CN / 10% 10mM NH₄CO₂ in water / 0.1% ammonia

Gradient Program

For method 5_95_pH=3

25 Time (min)	A%	B%	Flow	Curve
0.00	95.0	5.0	0.900	1
2.00	5.0	95.0	0.900	6
4.00	5.0	95.0	0.900	6
5.00	95.0	5.0	0.900	6

30

For method 5_95_pH=10

	Time (min)	A%	B%	Flow	Curve
	0.00	95.0	5.0	0.900	1
	2.00	5.0	95.0	0.900	6
5	4.00	5.0	95.0	0.900	6
	5.00	95.0	5.0	0.900	6

Preparative UV-HPLC

- The LC system comprises a Waters 2525 quaternary pump, a Waters 996 Photo Diode Array (PDA) detector, a Waters 2700 sample manager, a Column Fluidics Organiser and a Waters Fraction Collector operating in reverse phase at one of two pH systems.

Low pH system (approximately pH 3.2)

- 15 The reverse phase separation was carried out on a Luna C18 from Phenomenex 100 x 21.2 mm with 5 μ m silica.

Injection Volume 500 μ L

UV data 254 nm

Flow Rate 20 mL/min

- 20 Solvent A 90% water / 10% CH₃CN / 0.1% formic acid

Solvent B 90% CH₃CN / 10% water / 0.1% formic acid

High pH system (approximately pH 9.5)

- 25 The reverse phase separation was carried out on a Gemini C18 from Phenomenex 150 x 21.2 mm with 10 μ m silica.

Injection Volume 500 μ L

UV data 254nm

Flow Rate 20mL/min

- Solvent C 90% 10mM NH₄HCO₂ in water / 0.1% Ammonia / 10% CH₃CN
- 30 Solvent D 90% CH₃CN / 10% 10mM NH₄HCO₂ in water / 0.1% Ammonia

Typical gradient profiles are described below:

Gradient Program for Low pH Method

	Time	A%	B%	C%	D%	Flow	Curve
	0.00	95.0	5.0	0.0	0.0	20	1
	9.00	5.0	95.0	0.0	0.0	20	6
5	11.00	5.0	95.0	0.0	0.0	20	6
	11.50	95.0	5.0	0.0	0.0	20	6
	12.00	95.0	5.0	0.0	0.0	20	6

Gradient Program for High pH Method

	Time	A%	B%	C%	D%	Flow	Curve
	0.00	0.0	0.0	95.0	5.0	20	1
	9.00	0.0	0.0	5.0	95.0	20	6
	11.00	0.0	0.0	5.0	95.0	20	6
	11.50	0.0	0.0	95.0	5.0	20	6
15	12.00	0.0	0.0	95.0	5.0	20	6

INTERMEDIATE 1**2-Fluoro-4-iodo-1-isothiocyantobenzene**

- 20 Thiophosgene (3.55 mL, 46.4 mmol) was added to a rapidly-stirred mixture of 2-fluoro-4-iodoaniline (10.0 g, 42.2 mmol) in CHCl₃ (200 mL) and water (100 mL). The mixture was stirred at r.t. for 16 h. The organic phase was dried (Na₂SO₄) and concentrated *in vacuo* to give the *title compound* as an off-white crystalline solid (11.8 g, quant.). δ_H (DMSO-d₆) 7.87 (1H, dd, *J* 1.8, 9.5 Hz), 7.63 (1H, ddd, *J* 1.0, 1.8, 8.4 Hz),
- 25 7.25 (1H, dd, *J* 8.2, 8.4 Hz).

INTERMEDIATE 2**Ethyl 2-[(4-bromo-2-fluorophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylate**

- 30 Prepared from ethyl (2-chloropyridin-3-yl)acetate (D. H. Bremner *et al.*, *Synthesis*, 1997, 949) (500 mg, 2.5 mmol) and 4-bromo-2-fluorophenyl isothiocyanate (580 mg, 2.5 mmol) by the method of Example 1. *Title compound* obtained as an off-white solid (390 mg, 40%). δ_H (DMSO-d₆) 10.37 (1H, br s), 8.25 (1H, dd, *J* 1.4, 8.1 Hz),

8.19 (1H, d, J 4.8 Hz), 7.69 (1H, dd, J 1.8, 10.2 Hz), 7.56-7.45 (2H, m), 7.32 (1H, dd, J 4.5, 8.1 Hz), 4.35 (2H, q, J 7.1 Hz), 1.37 (3H, t, J 7.1 Hz). LCMS (ES⁺) RT 4.66 minutes, 395 (M(⁷⁹Br)+H)⁺.

5

INTERMEDIATE 3

3-(tert-Butyldimethylsilyloxy)propylamine

To a solution of *N*-(3-hydroxypropyl)phthalimide (5.25 g, 24.36 mmol) in DMF (20 mL) was added imidazole (16.6 g, 240 mmol) and *tert*-butyldimethylsilyl chloride (19 g, 120 mmol). The reaction was stirred at room temperature for 18 hours before the volatiles were removed *in vacuo* and a portion of the crude product was subjected to column chromatography (SiO₂, 1:1 DCM/hexanes) to give 2-[3-(*tert*-butyldimethylsilyloxy)propyl]isoindole-1,3-dione as a clear oil (5 g). 2-[3-(*tert*-Butyldimethylsilyloxy)propyl]isoindole-1,3-dione (5 g, 26.4 mmol) was dissolved in ethanol (50 ml) and methyl hydrazine (2.94 ml, 55.4 mmol) added. The reaction was heated to 75°C for 8 hours before concentration *in vacuo*. The crude residue was triturated with a mixture of diethyl ether (150 mL) and hexanes (50 mL) and the resultant solid removed by filtration. The solvents were removed *in vacuo* to give the *title compound* as a pale yellow oil (1.8 g, 61%). δ_H (DMSO-*d*₆) 4.58 (2H, br s), 3.63-3.58 (2H, m), 2.67-2.62 (2H, m), 1.60-1.55 (2H, m), 0.83 (9H, d, J 1.1 Hz), 0.00 (6H, d, J 1.2 Hz). LCMS (ES⁺) RT 1.77 minutes, 190 (M+H)⁺.

20

INTERMEDIATE 4

25 2-Methylsulfonylthieno[2,3-*b*]pyridine-3-carboxylic acid ethyl ester

To a solution of ethyl (2-chloropyridin-3-yl)acetate (D. H. Bremner *et al.*, *Synthesis*, 1997, 949) (8.0 g, 40.0 mmol) and carbon disulfide (3.18 g, 42.0 mmol) in DMSO (100 mL) was added sodium hydride portionwise (2.4 g, 60.0 mmol). After 60 minutes stirring at room temperature the mixture was heated at 80°C for 2 hours. After this time the reaction mixture was allowed to cool to room temperature and methyl iodide (7.6 g, 54.0 mmol) added. After 18 hours ice (50 mL) was added and a yellow precipitate formed which was isolated *via* filtration to give the *title compound* as a grey solid (7.95 g,

30

78%). δ_H (DMSO- d_6) 8.60 (1H, dd, J 1.6, 8.2 Hz), 8.46, (1H, dd, J 1.6, 4.6 Hz), 7.35 (1H, dd, J 4.6, 8.2 Hz), 4.48 (2H, q, J 7.1 Hz), 2.71, (3H, s), 1.49 (3H, t, J 7.1 Hz).

INTERMEDIATE 5

5

2-Methylsulfanyltieno[2,3-*b*]pyridine-3-carboxylic acid

A mixture of Intermediate 4 (12.5 g, 50.0 mmol) in THF (200 mL) and MeOH (50 mL) was treated with sodium hydroxide solution (10% solution in water, 50 mL) and stirred at room temperature for 18 h. After this time the reaction mixture was reduced *in vacuo* to one third of its volume. Water (50 mL) was then added before 10% HCl was added until a white precipitate formed. This was filtered to give the *title compound* as a crystalline white solid (10.6 g, 95%). δ_H (DMSO- d_6) 13.50-13.20 (1H br s), 8.55 (1H, dd, J 1.2, 8.2 Hz), 8.48 (1H, dd, J 1.3, 4.5 Hz), 7.49 (1H, dd, J 4.6, 8.2 Hz), 3.25 (3H, s).

15

INTERMEDIATE 6

2-Methanesulfinylthieno[2,3-*b*]pyridine-3-carboxylic acid

Oxone (14.5 g, 24.0 mmol) dissolved in water (25 mL) was added to a rapidly stirred mixture of Intermediate 5 (10.6 g, 47 mmol) in MeOH (250 mL). The mixture was stirred at room temperature for 4 h. The reaction mixture was separated between DCM (300 mL) and water (200 mL). The organic layer was dried (Na₂SO₄) and concentrated *in vacuo* to give the *title compound* as a white crystalline solid (10.0 g, 88%). δ_H (DMSO- d_6) 14.20-13.80 (1H, br s), 8.73 (1H, dd, J 1.7, 8.3 Hz), 8.69 (1H, J 1.7, 4.6 Hz), 7.61 (1H, dd, J 4.6, 8.3 Hz), 3.05 (3H, s).

25

INTERMEDIATE 7

2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylic acid

To a stirred solution of 2-fluoro-4-iodoaniline (6.0 g, 25 mmol) in THF (100 mL) at 0°C (ice bath) was added LiHMDS (1.0 M solution in THF, 20.0 mL, 20.0 mmol) slowly. The mixture was allowed to stir at room temperature for 30 minutes before cooling to 0°C and Intermediate 6 (2.0 g, 8.3 mmol) was added portionwise. The mixture was stirred at room temperature for 1 hour. After this time the reaction mixture was

22
2X

poured onto ice and when at ambient temperature citric acid was added until a precipitate formed. The mixture was filtered to give the *title compound* as a pale brown crystalline solid (2.9 g, 84%). δ_H (DMSO- d_6) 14.00-13.00 (1H, br s), 10.80 (1H, s), 8.36 (1H, dd, J 1.3, 8.1 Hz), 8.32 (1H, dd, J 1.3, 4.8 Hz), 7.84 (1H, dd, J 1.8, 10.1 Hz), 7.69 (1H, d, J 8.3 Hz), 7.54 (1H, m), 7.42 (1H, dd, J 8.3, 4.8 Hz).

INTERMEDIATE 8

4-Iodo-1-isothiocyanato-2-methylbenzene

10 To a stirring solution of 4-iodo-2-methylaniline (1.0 g, 4.2 mmol) in DCM (50 mL) was added water (20 mL) followed by thiophosgene (490 mg, 4.2 mmol). The reaction mixture was stirred overnight before the layers were separated and the organic layer dried (Na_2SO_4) and evaporated *in vacuo* to give the desired product as a brown solid (1.05 g, 89%). δ_H ($CDCl_3$) 7.75 (1H, d, J 1.2 Hz), 7.62 (1H, dd, J 1.2, 8.3 Hz), 7.15 (1H, d, J 8.3 Hz), 2.20 (3H, s).

INTERMEDIATE 9

2-Chloro-4-iodo-1-isothiocyanatobenzene

20 To a stirred solution of 2-chloro-4-iodoaniline (1.0 g, 3.9 mmol) in DCM (50 mL) was added water (20 mL) followed by thiophosgene (476 mg, 4.1 mmol). The reaction mixture was stirred overnight before the layers were separated and the organic layer dried (Na_2SO_4) and evaporated *in vacuo* to give the desired product as a brown solid (1.0 g, 86%). δ_H ($CDCl_3$) 7.79 (1H, d, J 1.9 Hz), 7.58 (1H, dd, J 1.9, 8.4 Hz), 6.97 (1H, d, J 8.4 Hz).

INTERMEDIATE 10

30 (2R)-2-[(2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carbonyl)amino)-methyl]pyrrolidine-1-carboxylic acid *tert*-butyl ester

1-(3-Dimethylaminopropyl)-3-carbodiimide hydrochloride (139 mg, 0.72 mmol) was added to a solution of Intermediate 7 (150 mg, 0.36 mmol), 1-hydroxybenzotriazole (98 mg, 0.72 mmol), *N*-methylmorpholine (0.11 mL, 0.99 mmol) and (*R*)-2-

PETITORIO

AS: 107.898


Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-080917- -00000-0000

Fecha: 2008-08-04 17:03:26 Dep. 2020 NUECREACIONE
Ira. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 152**FORMULARIO ÚNICO DE SOLICITUD DE PATENTE**
PCT
ENTRADA EN FASE NACIONAL

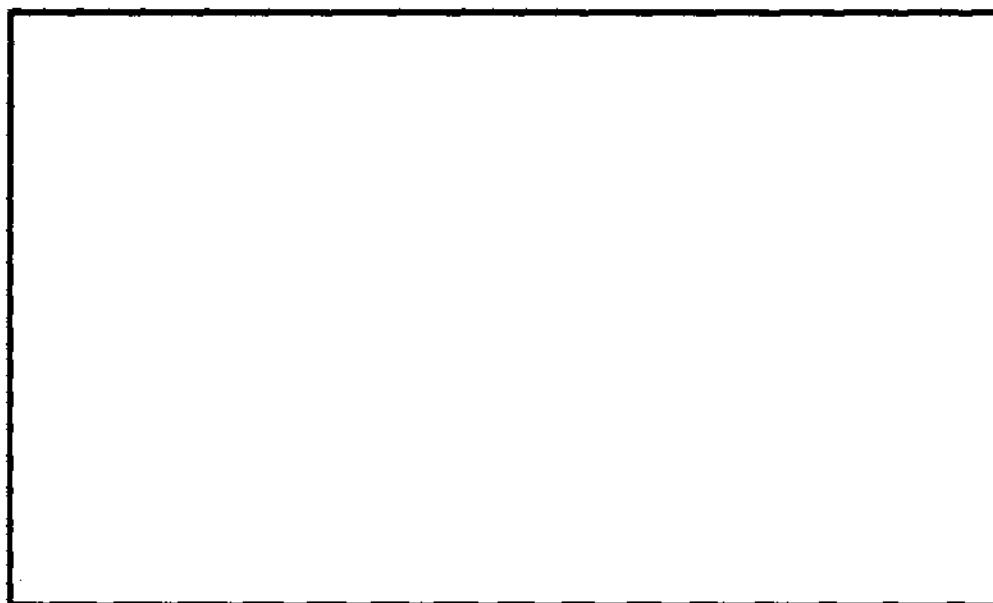
1 SOLICITUD DE:			
☒ Patente de Invención.		☐ Patente de Modelo de Utilidad.	
☒ Capítulo I.		☐ Capítulo II.	
2 SOLICITANTE (71)	Nombre: UCB PHARMA, S.A. Dirección: 60 Allée de la Recherche, B-1070, Bruselas, Bélgica Nacionalidad o Domicilio: Bélgica Lugar de Constitución: Bélgica Teléfono: Fax: E-mail		IDENTIFICACIÓN C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: JUAN PABLO CADENA SARMIENTO Dirección: Cra. 7 No. 71-21 Torre B – Piso 4, Bogotá, Colombia. Teléfono: 744-2200 Fax: 742-2200 E-mail:		IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>80.410.337</u> TP <u>57492</u>
4 INVENTOR (ES) (72)	Nombre: Martin Clive HUTCHINGS, Sarah Catherine ARCHIBALD, Daniel Christopher BROOKINGS, Jeremy Martin DAVIS, James Andrew JOHNSON, Barry John LANGHAM, Judi Charlotte NEUSS. Dirección: UCB Celltech, 208 Bath Road, Slough, Berkshire SL1 3WE, GB; UCB Celltech, 208 Bath Road, Slough, Berkshire SL1 3WE, GB; UCB Celltech, 208 Bath Road, Slough, Berkshire SL1 3WE, GB; UCB Celltech, 208 Bath Road, Slough, Berkshire SL1 3WE, GB; UCB Celltech, 208 Bath Road, Slough, Berkshire SL1 3WE, GB; UCB Celltech, 208 Bath Road, Slough, Berkshire SL1 3WE, GB; UCB Celltech, 208 Bath Road, Slough, Berkshire SL1 3WE, GB (Respectivamente). Nacionalidad o Domicilio: Gran Bretaña (Respectivamente).		
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6 Título (54): <u>DERIVADOS DE TIENO-PIRIDINA COMO INHIBIDORES DE MEK</u>			
7 Clasificación Internacional (51): _____			
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9 Comprobante de pago No. <u>08-44.576</u> Fecha <u>01-08-2008</u>			
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.			

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$ 501.000
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. **Fotocopia autenticada**
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: Tarjeta de Propietarios
Documentos PCT

11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente,

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA:

C.C. 80.410.337 de Usaquén TP 57492 del C.S.J.

7

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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FECHA : JUNIO 5 DE 2008

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BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO DE BOGOTA	062754387	3255976	04/06/2008	53,900,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
50005-01-01	SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	501,000.00
		TOTAL :	\$ 501,000.00

QUINIENTOS UN MIL PESOS

RESPONSABLE : _____

[Signature]

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4

4
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

PATENTE ☒ **PCT/GB2007/000310** **MODELO DE UTILIDAD** ☐ **DISEÑO INDUSTRIAL** ☐

SOLICITANTE/S. RAZON SOCIAL O APELLIDOS Y NOMBRES UCB PHARMA, S.A.

DOMICILIO BRUSELAS, BELGICA

APODERADO JUAN PABLO CADENA SARMIENTO

TITULO DERIVADOS DE TIENO-PIRIDINA, COMO INHIBIDORES DE MEK

CLASIFICACION _____

EXPEDIENTE No. _____ **FECHA DE SOLICITUD** _____ **ROLLO MICROFILM** _____

CERTIFICADO No. _____ **FECHA DE CONCESION** _____ **VIGENCIA DESDE** _____ **HASTA** _____

PRORROGA _____ **CAMBIO DE NOMBRE** _____

TRASPASO A _____

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OTROS BROOKINGS, JEREMY MARTIN DAVIS, JAMES ANDREW JOHNSON, BARRY JOHN LANGHAM Y OTROS

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(71) Applicant (for all designated States except US): UCB PHARMA S.A. [BE/BE]; 60 Allée De La Recherche, B-1070 Brussels (BE).

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(54) Title: THIENO-PYRIDINE DERIVATIVES AS MEK INHIBITORS

(57) Abstract: A series of thieno[2,3-*b*]pyridine derivatives which are substituted in the 2- position by a substituted anilino moiety, being selective inhibitors of human MEK (MAPKK) enzymes, are accordingly of benefit in medicine, for example in the treatment of inflammatory, autoimmune, cardiovascular, proliferative (including oncological) and nociceptive conditions.

WO 2007/088345 A1

THIENO-PYRIDINE DERIVATIVES AS MEK INHIBITORS

The present invention relates to a class of thieno-pyridine derivatives and to their use in therapy. More particularly, the invention is concerned with thieno[2,3-*b*]pyridine derivatives which are substituted in the 2-position by a substituted anilino moiety. These compounds are selective inhibitors of MEK (MAPKK) enzymes, and are accordingly of benefit as pharmaceutical agents, especially in the treatment of adverse inflammatory, autoimmune, cardiovascular, proliferative (including oncological) and nociceptive conditions.

MEK enzymes are implicated in a variety of physiological and pathological functions that are believed to be operative in a range of human diseases. These functions are summarised in paragraphs [0004] and [0005] of US 2005/0049276 A1.

The compounds of use in the present invention, being potent and selective MEK inhibitors, are therefore beneficial in the treatment and/or prevention of various human ailments. These include autoimmune and inflammatory disorders such as rheumatoid arthritis, osteoarthritis, multiple sclerosis, asthma, inflammatory bowel disease, psoriasis and transplant rejection; cardiovascular disorders including thrombosis, cardiac hypertrophy, hypertension, and irregular contractility of the heart (e.g. during heart failure); proliferative disorders such as restenosis, and oncological conditions including leukaemia, glioblastoma, lymphoma, melanoma, and human cancers of the liver, bone, skin, brain, pancreas, lung, breast, stomach, colon, rectum, prostate, ovary and cervix; and pain and nociceptive disorders, including chronic pain and neuropathic pain.

In addition, the compounds of use in the present invention may be beneficial as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents. Thus, the compounds of use in this invention may be useful as radioligands in assays for detecting compounds capable of binding to human MEK enzymes.

MEK inhibitors based on a fused bicyclic aromatic ring system attached to a substituted anilino moiety are known from the art. Examples of relevant publications include WO 2005/051906, WO 2005/023251, US-A-2005/0049276, WO 2005/009975, WO 03/077914 and WO 03/077855.

WO 2005/023818 describes a broad-ranging class of compounds based on a fused bicyclic aromatic ring system, which generically encompasses thieno-pyridine derivatives

attached to a substituted anilino moiety but nowhere specifically discloses any precise compound of this type. No discrete pharmacological activity, in terms of an identifiable pharmacological mechanism, is ascribed to the compounds described therein, but they are nevertheless stated to be useful *inter alia* in the treatment of cell proliferative diseases

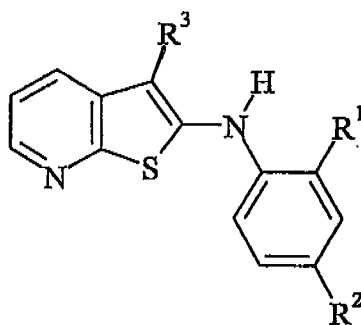
5 such as cancer. US-A-2003/0220365 is also of relevance in a related context.

Nowhere in the prior art, however, is there the precise disclosure of a class of thieno[2,3-*b*]pyridine derivatives attached at the 2-position to a substituted anilino moiety. It has now been found that such compounds are particularly valuable as selective inhibitors of MEK enzymes.

10 The compounds of the present invention are potent and selective MEK inhibitors having a binding affinity (IC_{50}) for the human MEK1 and/or MEK2 enzyme of 50 μ M or less, generally of 20 μ M or less, usually of 5 μ M or less, typically of 1 μ M or less, suitably of 500 nM or less, ideally of 100 nM or less, and preferably of 20 nM or less (the skilled person will appreciate that a *lower* IC_{50} figure denotes a *more active* compound).

15 The compounds of the invention may possess at least a 10-fold selective affinity, typically at least a 20-fold selective affinity, suitably at least a 50-fold selective affinity, and ideally at least a 100-fold selective affinity, for the human MEK1 and/or MEK2 enzyme relative to other human kinases.

The present invention provides a compound of formula (I), or a pharmaceutically acceptable salt, solvate or *N*-oxide thereof:



(I)

wherein

25 R^1 represents hydrogen, halogen or C_{1-6} alkyl;

R^2 represents halogen or C_{1-6} alkyl;

R^3 represents hydrogen, cyano, $-CO_2R^a$, $-CONR^bR^c$ or $-CON(OR^b)R^c$;

R^a represents C₁₋₆ alkyl;

R^b represents hydrogen; or C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents; and

R^c represents hydrogen or C₁₋₆ alkyl (optionally substituted by hydroxy); or

R^b and R^c, when taken together with the nitrogen atom to which they are both attached, represent azetidiny, pyrrolidiny, piperidiny, morpholiny, thiomorpholiny, piperaziny, homopiperidiny, homomorpholiny or homopiperaziny, any of which groups may be optionally substituted by one or more substituents.

The present invention also provides a compound of formula (I) as depicted above, or a pharmaceutically acceptable salt, solvate or *N*-oxide thereof, wherein

R¹ and R² are as defined above;

R³ represents cyano, -CO₂R^a, -CONR^bR^c or -CON(OR^b)R^c;

R^a represents C₁₋₆ alkyl;

R^b represents hydrogen; or C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents; and

R^c represents hydrogen or C₁₋₆ alkyl; or

R^b and R^c, when taken together with the nitrogen atom to which they are both attached, represent azetidiny, pyrrolidiny, piperidiny, morpholiny, thiomorpholiny, piperaziny, homopiperidiny or homomorpholiny, any of which groups may be optionally substituted by one or more substituents.

For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound of the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, e.g. carboxy,

suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The present invention includes within its scope solvates of the compounds of formula (I) above. Such solvates may be formed with common organic solvents, e.g. hydrocarbon solvents such as benzene or toluene; chlorinated solvents such as chloroform or dichloromethane; alcoholic solvents such as methanol, ethanol or isopropanol; ethereal solvents such as diethyl ether or tetrahydrofuran; or ester solvents such as ethyl acetate. Alternatively, the solvates of the compounds of formula (I) may be formed with water, in which case they will be hydrates.

Suitable alkyl groups which may be present on the compounds of the invention include straight-chained and branched C₁₋₆ alkyl groups, for example C₁₋₄ alkyl groups. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl, butyl and pentyl groups. Particular alkyl groups include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl and 2,2-dimethylpropyl. Derived expressions such as "C₁₋₆ alkoxy", "C₁₋₆ alkylthio", "C₁₋₆ alkylsulphonyl" and "C₁₋₆ alkylamino" are to be construed accordingly.

Specific C₃₋₇ cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Suitable aryl groups include phenyl and naphthyl, preferably phenyl.

Suitable aryl(C₁₋₆)alkyl groups include benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

Suitable heterocycloalkyl groups, which may comprise benzo-fused analogues thereof, include azetidiny, tetrahydrofuranyl, dioxolanyl, pyrrolidinyl, indolinyl, imidazolidinyl, tetrahydropyranyl, piperidinyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, piperazinyl, morpholinyl and thiomorpholinyl.

Suitable heteroaryl groups include furyl, benzofuryl, dibenzofuryl, thienyl, benzothienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl and pyrazinyl groups.

The term "halogen" as used herein is intended to include fluorine, chlorine, bromine and iodine atoms.

Where the compounds of formula (I) have one or more asymmetric centres, they may accordingly exist as enantiomers. Where the compounds of the invention possess two or more asymmetric centres, they may additionally exist as diastereomers. The invention is to be understood to extend to all such enantiomers and diastereomers, and to mixtures thereof in any proportion, including racemates. Formula (I) and the formulae depicted hereinafter are intended to represent all individual stereoisomers and all possible mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (I) may exist as tautomers, for example keto ($\text{CH}_2\text{C}=\text{O}$)-enol ($\text{CH}=\text{CHOH}$) tautomers. Formula (I) and the formulae depicted hereinafter are intended to represent all individual tautomers and all possible mixtures thereof, unless stated or shown otherwise.

In one embodiment, R^1 represents hydrogen. In another embodiment, R^1 represents halogen, particularly fluoro or chloro, especially fluoro. In a further embodiment, R^1 represents C_{1-6} alkyl, especially methyl.

Typically, R^1 is fluoro.

In one embodiment, R^2 represents halogen, especially bromo or iodo. In another embodiment, R^2 represents C_{1-6} alkyl, especially methyl.

In one specific embodiment, R^2 is bromo. In another specific embodiment, R^2 is iodo.

Suitably, R^a represents methyl or ethyl, especially ethyl.

Favourably, R^b represents hydrogen; or C_{1-6} alkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl or C_{3-7} heterocycloalkyl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

Suitably, R^b represents hydrogen; or C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents.

Suitably, the group R^b , or the cyclic moiety $-\text{NR}^b\text{R}^c$, may be unsubstituted, or substituted by one or more substituents, typically by one or two substituents. In one embodiment, the group R^b , or the cyclic moiety $-\text{NR}^b\text{R}^c$, is unsubstituted. In another embodiment, the group R^b , or the cyclic moiety $-\text{NR}^b\text{R}^c$, is monosubstituted. In a further embodiment, the group R^b , or the cyclic moiety $-\text{NR}^b\text{R}^c$, is disubstituted.

Examples of typical substituents on R^b , or on the cyclic moiety $-\text{NR}^b\text{R}^c$, include C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, hydroxy(C_{1-6})alkyl, amino(C_{1-6})alkyl, (amino)(hydroxy)-(C_{1-6})alkyl, halogen, oxo, C_{2-6} alkylcarbonyl, carboxy, C_{2-6} alkoxy carbonyl,

di(C₁₋₆)alkylhydrazinylcarbonyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonylamino, aminocarbonylamino, aminocarbonyl, C₁₋₆ alkylaminocarbonyl, di(C₁₋₆)alkylaminocarbonyl, aminosulfonyl, C₁₋₆ alkylsulfonyl and C₁₋₆ alkylaminocarbonyl(C₁₋₆)alkyl. Further examples include C₁₋₆ alkoxy(C₁₋₆)alkyl, 5 carboxy(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, C₂₋₆ alkoxycarbonylamino and C₂₋₆ alkoxycarbonylamino(C₁₋₆)alkyl.

Examples of particular substituents on R^b, or on the cyclic moiety -NR^bR^c, include methyl, methoxy, hydroxy, hydroxymethyl, 2-hydroxyethyl, aminomethyl, 2-amino-3-hydroxypropyl, fluoro, oxo, acetyl, carboxy, methoxycarbonyl, ethoxycarbonyl, *tert*-10 butoxycarbonyl, dimethylhydrazinylcarbonyl, amino, methylamino, 1,3-dimethylbutylamino, dimethylamino, acetylamino, aminocarbonylamino, aminocarbonyl, ethylaminocarbonyl, diethylaminocarbonyl, aminosulfonyl, methylsulfonyl and methylaminocarbonylmethyl. Further examples include methoxymethyl, carboxymethyl, ethoxycarbonylmethyl, *tert*-butoxycarbonylamino and *tert*-butoxycarbonylaminomethyl.

15 Examples of favoured substituents on R^b, or on the cyclic moiety -NR^bR^c, include C₁₋₆ alkyl, C₁₋₆ alkoxy(C₁₋₆)alkyl, hydroxy, hydroxy(C₁₋₆)alkyl, amino, amino(C₁₋₆)alkyl, carboxymethyl, C₂₋₆ alkoxycarbonyl, C₂₋₆ alkoxycarbonyl(C₁₋₆)alkyl, di(C₁₋₆)alkylamino, C₂₋₆ alkoxycarbonylamino and C₂₋₆ alkoxycarbonylamino(C₁₋₆)alkyl.

Examples of specific substituents on R^b, or on the cyclic moiety -NR^bR^c, include 20 methyl, methoxymethyl, hydroxy, hydroxymethyl, 2-hydroxyethyl, amino, aminomethyl, carboxymethyl, *tert*-butoxycarbonyl, ethoxycarbonylmethyl, dimethylamino, *tert*-butoxycarbonylamino and *tert*-butoxycarbonylaminomethyl.

Favoured values of R^b include hydrogen, methyl, ethyl, propyl, cyclopropylmethyl, azetidiny, pyrrolidinyl, piperidinyl, azetidinylmethyl, dioxolanylmethyl, 25 pyrrolidinylmethyl, morpholinylethyl and morpholinylpropyl, any of which groups may be optionally substituted by one or more substituents. Favoured substituents in this context include C₁₋₆ alkyl (especially methyl), hydroxy, amino, C₂₋₆ alkoxycarbonyl (especially *tert*-butoxycarbonyl) and di(C₁₋₆)alkylamino (especially dimethylamino).

Specific values of R^b include hydrogen, methyl, 2-hydroxyethyl, 3-hydroxypropyl, 30 1-hydroxyprop-2-yl, 2,3-dihydroxypropyl, 2-amino-2-methylpropyl, 2,2-dimethyl-3-(dimethylamino)propyl, cyclopropylmethyl, 1-*tert*-butoxycarbonylazetidin-3-yl, pyrrolidin-3-yl, 1-*tert*-butoxycarbonylpyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, 1-methylpiperidin-4-yl, 1-*tert*-butoxycarbonylpiperidin-3-yl, 1-*tert*-butoxycarbonyl-

piperidin-4-yl, 1-*tert*-butoxycarbonylazetidin-3-ylmethyl, 2,2-dimethyl-[1,3]dioxolan-4-ylmethyl, pyrrolidin-2-ylmethyl, 2-(morpholin-4-yl)ethyl and 3-(morpholin-4-yl)propyl.

Typically, R^b represents hydrogen; or C_{1-6} alkyl, optionally substituted by one or more, preferably one or two, hydroxy groups.

5 Typical values of R^b include hydrogen, methyl, hydroxypropyl and dihydroxypropyl. In one embodiment, R^b represents hydrogen. In another embodiment, R^b represents methyl. In a further embodiment, R^b represents hydroxypropyl, especially 3-hydroxypropyl. In an additional embodiment, R^b represents dihydroxypropyl, especially 2,3-dihydroxypropyl.

10 In one embodiment, R^c is hydrogen. In another embodiment, R^c represents C_{1-6} alkyl, especially methyl. In a further embodiment, R^c represents hydroxy(C_{1-6})alkyl, e.g. hydroxyethyl (especially 2-hydroxyethyl).

Alternatively, the moiety $-NR^bR^c$ may suitably represent azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperazin-1-yl, homopiperidin-1-yl or homomorpholin-4-yl, any of which groups may be optionally substituted by one or
15 more substituents. The moiety $-NR^bR^c$ may also represent optionally substituted homopiperazin-1-yl.

Particular values for the cyclic moiety $-NR^bR^c$ include azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl and homopiperazin-1-yl, any of which
20 groups may be optionally substituted by one or more substituents.

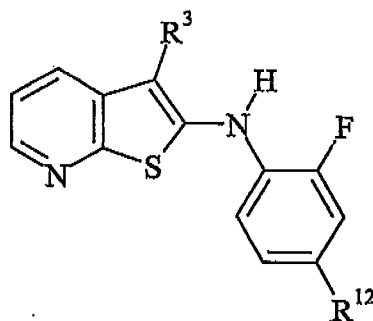
Specific values of the cyclic moiety $-NR^bR^c$ include 3-hydroxyazetidin-1-yl, 3-aminoazetidin-1-yl, 3-(aminomethyl)azetidin-1-yl, 3-(*tert*-butoxycarbonylamino)azetidin-1-yl, 3-(*tert*-butoxycarbonylaminomethyl)azetidin-1-yl, pyrrolidin-1-yl, 2-(methoxymethyl)pyrrolidin-1-yl, 3-hydroxypyrrolidin-1-yl, 3-aminopyrrolidin-1-yl, 3-(*tert*-
25 butoxycarbonylamino)pyrrolidin-1-yl, 2-(hydroxymethyl)piperidin-1-yl, 4-amino-piperidin-1-yl, 4-(*tert*-butoxycarbonylamino)piperidin-1-yl, morpholin-4-yl, 2-(hydroxymethyl)morpholin-4-yl, piperazin-1-yl, 4-methylpiperazin-1-yl, 2-(hydroxymethyl)-piperazin-1-yl, 4-(2-hydroxyethyl)piperazin-1-yl, 4-(carboxymethyl)piperazin-1-yl, 4-(*tert*-butoxycarbonyl)-2-(hydroxymethyl)piperazin-1-yl, 4-(ethoxycarbonylmethyl)-
30 piperazin-1-yl and homopiperazin-1-yl.

Suitably, the cyclic moiety $-NR^bR^c$ may be substituted by C_{1-6} alkyl, especially methyl. Particular values of $-NR^bR^c$ include pyrrolidin-1-yl, morpholin-4-yl and 4-methylpiperazin-1-yl.

Typically, R^3 represents cyano, $-\text{CO}_2R^a$, $-\text{CONR}^bR^c$, or $-\text{CON}(\text{OR}^b)R^c$, in which R^a , R^b and R^c are as defined above. Suitably, R^3 represents cyano, $-\text{CO}_2R^a$ or $-\text{CONR}^bR^c$, especially cyano or $-\text{CONR}^bR^c$, in which R^a , R^b and R^c are as defined above. Suitably, R^3 represents $-\text{CON}(\text{OR}^b)R^c$, in which R^b and R^c are as defined above.

5 In one embodiment, R^3 represents cyano. In another embodiment, R^3 represents $-\text{CO}_2R^a$, in which R^a is as defined above. In a further embodiment, R^3 represents $-\text{CONR}^bR^c$, in which R^b and R^c are as defined above. In an additional embodiment, R^3 represents $-\text{CON}(\text{OR}^b)R^c$, in which R^b and R^c are as defined above. In a still further embodiment, R^3 represents hydrogen.

10 A particular sub-group of compounds according to the invention is represented by the compounds of formula (II), and pharmaceutically acceptable salts, solvates and *N*-oxides thereof:



(II)

15 wherein

R^{12} represents halogen; and

R^3 is as defined above.

In one specific embodiment, R^{12} is bromo. In another specific embodiment, R^{12} is
20 iodo.

Specific novel compounds in accordance with the present invention include each of the compounds whose preparation is described in the accompanying Examples, and pharmaceutically acceptable salts and solvates thereof.

25 The present invention also provides a pharmaceutical composition which comprises a compound of formula (I) as defined above, or a pharmaceutically acceptable salt, solvate or *N*-oxide thereof, in association with one or more pharmaceutically acceptable carriers.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical, ophthalmic or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, 5 for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methyl cellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogenphosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycolate); or wetting 10 agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as 15 suspending agents, emulsifying agents, non-aqueous vehicles or preservatives. The preparations may also contain buffer salts, flavouring agents, colouring agents or sweetening agents, as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

20 For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of formula (I) may be formulated for parenteral administration by injection, e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoules or multi-dose containers, e.g. glass vials. The 25 compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

30 In addition to the formulations described above, the compounds of formula (I) may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds according to the present invention may be conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, fluorotrichloromethane, dichlorotetrafluoroethane, carbon
5 dioxide or other suitable gas or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

For topical administration the compounds according to the present invention may
10 be conveniently formulated in a suitable ointment containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, liquid petroleum, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax and water. Alternatively, the compounds according to the present invention may be formulated in a suitable lotion
15 containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, benzyl alcohol, 2-octyldodecanol and water.

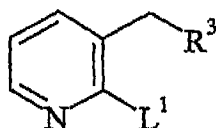
For ophthalmic administration the compounds according to the present invention
20 may be conveniently formulated as microionized suspensions in isotonic, pH-adjusted sterile saline, either with or without a preservative such as a bactericidal or fungicidal agent, for example phenylmercuric nitrate, benzylalkonium chloride or chlorhexidine acetate. Alternatively, for ophthalmic administration compounds may be formulated in an ointment such as petrolatum.

For rectal administration the compounds according to the present invention may
25 be conveniently formulated as suppositories. These can be prepared by mixing the active component with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and so will melt in the rectum to release the active component. Such materials include, for example, cocoa butter, beeswax and polyethylene glycols.

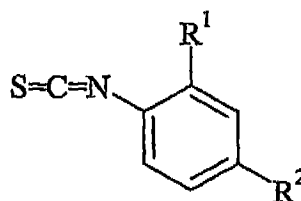
30 The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen and the condition of the patient to be treated. In general, however, daily dosages may range from around 10 ng/kg to 1000 mg/kg, typically from 100 ng/kg to 100 mg/kg, e.g. around 0.01

mg/kg to 40 mg/kg body weight, for oral or buccal administration, from around 10 ng/kg to 50 mg/kg body weight for parenteral administration, and from around 0.05 mg to around 1000 mg, e.g. from around 0.5 mg to around 1000 mg, for nasal administration or administration by inhalation or insufflation.

- 5 The compounds of formula (I) above, and the *N*-oxides thereof, may be prepared by a process which comprises reacting a compound of formula (III), or an *N*-oxide thereof, with a compound of formula (IV):



(III)



(IV)

10

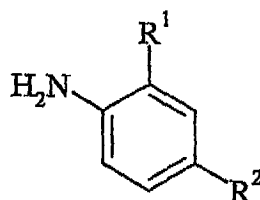
wherein R^1 , R^2 and R^3 are as defined above, and L^1 represents a suitable leaving group.

The leaving group L^1 is typically a halogen atom, e.g. chloro.

- The reaction is conveniently effected, at an elevated temperature if necessary, in a suitable solvent, e.g. dimethylsulphoxide, typically under basic conditions, e.g. in the presence of an inorganic base such as sodium hydride.

15

The intermediates of formula (IV) above may be prepared by reacting a compound of formula (V):



(V)

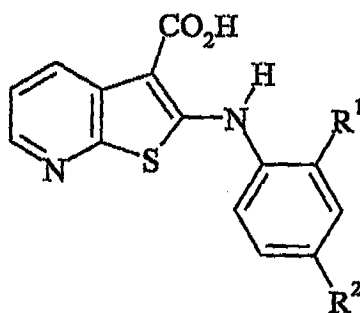
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wherein R^1 and R^2 are as defined above; with thiophosgene.

The reaction is conveniently effected in a suitable solvent, typically a mixture of chloroform and water.

In another procedure, the compounds of formula (I) above wherein R^3 represents $-\text{CONR}^b\text{R}^c$ or $-\text{CON}(\text{OR}^b)\text{R}^c$, and the *N*-oxides thereof, may be prepared by a process which comprises reacting a compound of formula $\text{H-NR}^b\text{R}^c$ or $\text{H-N}(\text{OR}^b)\text{R}^c$ with a compound of formula (VI), or an *N*-oxide thereof:

5

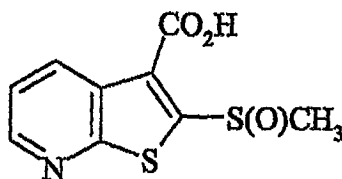


(VI)

wherein R^1 , R^2 , R^b and R^c are as defined above; in the presence of a condensing agent.

A suitable condensing agent is 1-(3-dimethylaminopropyl)-3-carbodiimide hydrochloride (EDC), in which case the reaction is conveniently effected in the presence of 1-hydroxybenzotriazole (HOBT) and *N*-methylmorpholine (NMM).

The compounds of formula (VI) above may be prepared by reacting the compound of formula (VII):



(VII)

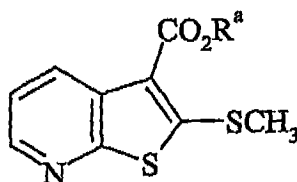
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with a compound of formula (V) as defined above.

The reaction may conveniently be effected by treating compound (V) with a base, e.g. lithium bis(trimethylsilyl)amide, in a suitable solvent, e.g. tetrahydrofuran, followed by the addition of compound (VII).

20

The intermediate of formula (VII) above may be prepared from a compound of formula (VIII):



(VIII)

wherein R^a is as defined above; by saponification of the ester moiety followed by
5 oxidation of the methylsulfanyl group.

Saponification of the ester moiety $-CO_2R^a$ in compound (VIII) may be effected by treatment with an alkaline base, e.g. sodium hydroxide, in a suitable solvent, e.g. an aqueous mixture of a lower alkanol such as methanol and a cyclic ether such as tetrahydrofuran. Oxidation of the methylsulfanyl group in the resulting compound may
10 then be effected by treatment with a suitable oxidising agent, e.g. Oxone® (potassium peroxymonosulfate), in an appropriate solvent, e.g. aqueous methanol.

The intermediates of formula (VIII) above may be prepared by reacting a compound of formula (III), wherein R^3 is $-CO_2R^a$ as defined above, with carbon disulfide, followed by treatment with a methyl halide such as iodomethane.

15 The reaction is conveniently effected in a suitable solvent, e.g. dimethylsulfoxide, in the presence of a base such as sodium hydride.

Where they are not commercially available, the starting materials of formula (III) and (V) may be prepared by methods analogous to those described in the accompanying Examples, or by standard methods well known from the art.

20 It will be understood that any compound of formula (I) initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula (I) by techniques known from the art. By way of example, a compound of formula (I) wherein R^3 represents $-CO_2R^a$ may be converted into the corresponding compound wherein R^3 represents $-CONH_2$ by treatment with ammonia, typically in a lower alkanol solvent, e.g. ethanol, at elevated temperature and pressure.
25 Alternatively, a compound of formula (I) wherein R^3 represents $-CO_2R^a$ may be converted into the corresponding compound wherein R^3 represents $-CONR^bR^c$ by treatment with the appropriate amine of formula $H-NR^bR^c$ in the presence of trimethylaluminium. A compound of formula (I) wherein R^3 represents $-CO_2R^a$ may be converted into the

- corresponding compound wherein R^3 represents hydrogen by treatment with an alkaline reagent such as lithium hydroxide under forcing conditions, e.g. by heating at reflux in a mixture of ethanol and water. A compound of formula (I) wherein R^3 contains a 2,2-dimethyl-[1,3]dioxolan-4-ylmethyl moiety may be converted into the corresponding
- 5 compound wherein R^3 contains a 2,3-dihydroxypropyl moiety by treatment with a mineral acid such as hydrochloric acid. A compound of formula (I) wherein R^3 contains a nitrogen atom to which a *tert*-butoxycarbonyl (BOC) group is attached may be converted into the corresponding compound wherein R^3 contains an N-H functionality by treatment with an acid, e.g. a mineral acid such as hydrochloric acid, or an organic acid such as
- 10 trifluoroacetic acid. A compound of formula (I) wherein R^3 contains an N-H functionality may be converted into the corresponding compound wherein R^3 contains a nitrogen atom to which an ethoxycarbonylmethyl group is attached by treatment with ethyl chloroacetate, typically in the presence of triethylamine; the resulting compound may then be converted into the corresponding compound wherein R^3 contains a nitrogen
- 15 atom to which a carboxymethyl group is attached by treatment with an alkaline reagent such as sodium hydroxide, typically in an aqueous solution of a lower alkanol such as ethanol. The pyridine-*N*-oxide derivative of a compound of formula (I) may be converted into the corresponding compound of formula (I) by treatment with triphenyl phosphine and phosphorus trichloride.
- 20 Where a mixture of products is obtained from any of the processes described above for the preparation of compounds according to the invention, the desired product can be separated therefrom at an appropriate stage by conventional methods such as preparative HPLC; or column chromatography utilising, for example, silica and/or alumina in conjunction with an appropriate solvent system.
- 25 Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques. In particular, where it is desired to obtain a particular enantiomer of a compound of formula (I) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for
- 30 resolving enantiomers. Thus, for example, diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (I), e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation, and the desired enantiomer

recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt. In another resolution process a racemate of formula (I) may be separated using chiral HPLC. Moreover, if desired, a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above. Alternatively, a particular enantiomer may be obtained by performing an enantiomer-specific enzymatic biotransformation, e.g. an ester hydrolysis using an esterase, and then purifying only the enantiomerically pure hydrolysed acid from the unreacted ester antipode.

Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 3rd edition, 1999. The protecting groups may be removed at any convenient subsequent stage utilising methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds in accordance with this invention potentially inhibit the activity of human MEK enzyme.

In vitro MEK assay

MEK1 activity was measured in a cascade assay initiated by active Raf, via activation of MEK, Erk2 and subsequent phosphorylation of fluorescein-labelled Erk-tide substrate in an assay based on fluorescence polarisation (IMAP). The assay was carried out in 20mM Tris + 5mM MgCl₂ + 2mM DL-dithiothreitol + 0.01% Tween 20 pH 7.2, containing 1.5nM unactive MEK, 100nM unactive Erk and 200nM Erk-tide (all concentrations are final concentrations). Compounds, or DMSO controls, were tested at a final concentration of 2% DMSO, and the assay initiated in the presence of 5μM ATP by addition of 1.25nM active Raf in assay buffer. After 20 min at r.t., stop solution was added followed by IMAP binding beads, the assay mixture was then incubated for 90 min at r.t. (with shaking) and then read on a Molecular Devices LJM HT reader.

When tested in the above assay, the compounds of the accompanying Examples were all found to inhibit human MEK enzyme with IC₅₀ values of 10 µM or better.

EXAMPLES

5

Abbreviations used

EtOAc - ethyl acetate	DMSO - dimethylsulphoxide
THF - tetrahydrofuran	DCM - dichloromethane
ether - diethyl ether	CDCl ₃ - deuteriochloroform
10 MeOH - methanol	MeCN - acetonitrile
EtOH - ethanol	ES - electrospray
DMF - <i>N,N</i> -dimethylformamide	HOBT - 1-hydroxybenzotriazole
SiO ₂ - silica	NMM - <i>N</i> -methylmorpholine
h - hour(s)	min - minute(s)
15 r.t. - room temperature	aq - aqueous
sat. - saturated	RT - retention time
BOC - <i>tert</i> -butoxycarbonyl	LiHMDS - lithium bis(trimethylsilyl)amide
MCPBA - 3-chloroperoxybenzoic acid	
EDC - 1-(3-dimethylaminopropyl)-3-carbodiimide hydrochloride	

20

All NMR spectra were obtained either at 300 MHz or 400 MHz.

Compounds were named with the aid of ACD Labs Name (v. 7.0) supplied by Advanced Chemical Development, Toronto, Canada.

25 *Standard LCMS method*

The LC-MS system used comprises a Waters Alliance 2795 HT quaternary HPLC, Waters 996 Photo Diode Array (PDA) detector and Waters ZQ 4000 single quadrupole mass spectrometer. The ZQ can acquire data simultaneously in positive and negative electrospray ionisation modes.

30

ZQ Mass Spectrometer

Capillary	3.5kV	Cone	50V
Extractor	2V	Source Temp	80°C

Desolvation Temp	200°C	Cone Gas	150 L/h
Desolvation Gas	250 L/h	Multiplier	650V

Data were acquired in a full scan from 100 to 1000 m/z.

Scan duration	0.80 s
5 Interscan delay	0.20 s

HPLC

Analytical reverse phase separation was carried out on a Gemini C18 from Phenomenex 50 x 4.6 mm with 5 µm silica.

10

Injection Volume	5 µL
UV data	240 to 400 nm
Sample Temperature	20°C
Column Temperature	30°C

15 Flow Rate	0.9 mL/min
Split to ZQ	~0.40 mL/min

Solvent A: 90% 10mM NH₄CO₂ in water / 0.1% formic acid / 10% CH₃CN

Solvent B: 90% CH₃CN / 0.1% formic acid / 10% 10mM NH₄CO₂ in water

20 Solvent C: 90% 10mM NH₄CO₂ in water / 0.1% ammonia / 10% CH₃CN

Solvent D: 90% CH₃CN / 10% 10mM NH₄CO₂ in water / 0.1% ammonia

Gradient Program

For method 5_95_pH=3

25 Time (min)	A%	B%	Flow	Curve
0.00	95.0	5.0	0.900	1
2.00	5.0	95.0	0.900	6
4.00	5.0	95.0	0.900	6
5.00	95.0	5.0	0.900	6

30

For method 5_95_pH=10

	Time (min)	A%	B%	Flow	Curve
	0.00	95.0	5.0	0.900	1
	2.00	5.0	95.0	0.900	6
5	4.00	5.0	95.0	0.900	6
	5.00	95.0	5.0	0.900	6

Preparative UV-HPLC

- The LC system comprises a Waters 2525 quaternary pump, a Waters 996 Photo Diode Array (PDA) detector, a Waters 2700 sample manager, a Column Fluidics Organiser and a Waters Fraction Collector operating in reverse phase at one of two pH systems.

Low pH system (approximately pH 3.2)

- 15 The reverse phase separation was carried out on a Luna C18 from Phenomenex 100 x 21.2 mm with 5 µm silica.

Injection Volume 500 µL

UV data 254 nm

Flow Rate 20 mL/min

- 20 Solvent A 90% water / 10% CH₃CN / 0.1% formic acid

Solvent B 90% CH₃CN / 10% water / 0.1% formic acid

High pH system (approximately pH 9.5)

- 25 The reverse phase separation was carried out on a Gemini C18 from Phenomenex 150 x 21.2 mm with 10 µm silica.

Injection Volume 500 µL

UV data 254nm

Flow Rate 20mL/min

- Solvent C 90% 10mM NH₄HCO₂ in water / 0.1% Ammonia / 10% CH₃CN
- 30 Solvent D 90% CH₃CN / 10% 10mM NH₄HCO₂ in water / 0.1% Ammonia

Typical gradient profiles are described below:

Gradient Program for Low pH Method

	Time	A%	B%	C%	D%	Flow	Curve
	0.00	95.0	5.0	0.0	0.0	20	1
	9.00	5.0	95.0	0.0	0.0	20	6
5	11.00	5.0	95.0	0.0	0.0	20	6
	11.50	95.0	5.0	0.0	0.0	20	6
	12.00	95.0	5.0	0.0	0.0	20	6

Gradient Program for High pH Method

	Time	A%	B%	C%	D%	Flow	Curve
	0.00	0.0	0.0	95.0	5.0	20	1
	9.00	0.0	0.0	5.0	95.0	20	6
	11.00	0.0	0.0	5.0	95.0	20	6
	11.50	0.0	0.0	95.0	5.0	20	6
15	12.00	0.0	0.0	95.0	5.0	20	6

INTERMEDIATE 1**2-Fluoro-4-iodo-1-isothiocyantobenzene**

- 20 Thiophosgene (3.55 mL, 46.4 mmol) was added to a rapidly-stirred mixture of 2-fluoro-4-iodoaniline (10.0 g, 42.2 mmol) in CHCl₃ (200 mL) and water (100 mL). The mixture was stirred at r.t. for 16 h. The organic phase was dried (Na₂SO₄) and concentrated *in vacuo* to give the *title compound* as an off-white crystalline solid (11.8 g, quant.). δ_{H} (DMSO-d₆) 7.87 (1H, dd, *J* 1.8, 9.5 Hz), 7.63 (1H, ddd, *J* 1.0, 1.8, 8.4 Hz),
- 25 7.25 (1H, dd, *J* 8.2, 8.4 Hz).

INTERMEDIATE 2**Ethyl 2-[(4-bromo-2-fluorophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylate**

- 30 Prepared from ethyl (2-chloropyridin-3-yl)acetate (D. H. Bremner *et al.*, *Synthesis*, 1997, 949) (500 mg, 2.5 mmol) and 4-bromo-2-fluorophenyl isothiocyanate (580 mg, 2.5 mmol) by the method of Example 1. *Title compound* obtained as an off-white solid (390 mg, 40%). δ_{H} (DMSO-d₆) 10.37 (1H, br s), 8.25 (1H, dd, *J* 1.4, 8.1 Hz),

8.19 (1H, d, J 4.8 Hz), 7.69 (1H, dd, J 1.8, 10.2 Hz), 7.56-7.45 (2H, m), 7.32 (1H, dd, J 4.5, 8.1 Hz), 4.35 (2H, q, J 7.1 Hz), 1.37 (3H, t, J 7.1 Hz). LCMS (ES⁺) RT 4.66 minutes, 395 (M(⁷⁹Br)+H)⁺.

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INTERMEDIATE 3

3-(*tert*-Butyldimethylsilyloxy)propylamine

To a solution of *N*-(3-hydroxypropyl)phthalimide (5.25 g, 24.36 mmol) in DMF (20 mL) was added imidazole (16.6 g, 240 mmol) and *tert*-butyldimethylsilyl chloride (19 g, 120 mmol). The reaction was stirred at room temperature for 18 hours before the volatiles were removed *in vacuo* and a portion of the crude product was subjected to column chromatography (SiO₂, 1:1 DCM/hexanes) to give 2-[3-(*tert*-butyldimethylsilyloxy)propyl]isoindole-1,3-dione as a clear oil (5 g). 2-[3-(*tert*-Butyldimethylsilyloxy)propyl]isoindole-1,3-dione (5 g, 26.4 mmol) was dissolved in ethanol (50 ml) and methyl hydrazine (2.94 ml, 55.4 mmol) added. The reaction was heated to 75°C for 8 hours before concentration *in vacuo*. The crude residue was triturated with a mixture of diethyl ether (150 mL) and hexanes (50 mL) and the resultant solid removed by filtration. The solvents were removed *in vacuo* to give the *title compound* as a pale yellow oil (1.8 g, 61%). δ_H (DMSO-*d*₆) 4.58 (2H, br s), 3.63-3.58 (2H, m), 2.67-2.62 (2H, m), 1.60-1.55 (2H, m), 0.83 (9H, d, J 1.1 Hz), 0.00 (6H, d, J 1.2 Hz). LCMS (ES⁺) RT 1.77 minutes, 190 (M+H)⁺.

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INTERMEDIATE 4

2-Methylsulfanyltieno[2,3-*b*]pyridine-3-carboxylic acid ethyl ester

To a solution of ethyl (2-chloropyridin-3-yl)acetate (D. H. Bremner *et al.*, *Synthesis*, 1997, 949) (8.0 g, 40.0 mmol) and carbon disulfide (3.18 g, 42.0 mmol) in DMSO (100 mL) was added sodium hydride portionwise (2.4 g, 60.0 mmol). After 60 minutes stirring at room temperature the mixture was heated at 80°C for 2 hours. After this time the reaction mixture was allowed to cool to room temperature and methyl iodide (7.6 g, 54.0 mmol) added. After 18 hours ice (50 mL) was added and a yellow precipitate formed which was isolated *via* filtration to give the *title compound* as a grey solid (7.95 g,

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78%). δ_H (DMSO- d_6) 8.60 (1H, dd, J 1.6, 8.2 Hz), 8.46, (1H, dd, J 1.6, 4.6 Hz), 7.35 (1H, dd, J 4.6, 8.2 Hz), 4.48 (2H, q, J 7.1 Hz), 2.71, (3H, s), 1.49 (3H, t, J 7.1 Hz).

INTERMEDIATE 5

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2-Methylsulfanylthieno[2,3-*b*]pyridine-3-carboxylic acid

A mixture of Intermediate 4 (12.5 g, 50.0 mmol) in THF (200 mL) and MeOH (50 mL) was treated with sodium hydroxide solution (10% solution in water, 50 mL) and stirred at room temperature for 18 h. After this time the reaction mixture was reduced *in vacuo* to one third of its volume. Water (50 mL) was then added before 10% HCl was added until a white precipitate formed. This was filtered to give the *title compound* as a crystalline white solid (10.6 g, 95%). δ_H (DMSO- d_6) 13.50-13.20 (1H br s), 8.55 (1H, dd, J 1.2, 8.2 Hz), 8.48 (1H, dd, J 1.3, 4.5 Hz), 7.49 (1H, dd, J 4.6, 8.2 Hz), 3.25 (3H, s).

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INTERMEDIATE 6

2-Methanesulfinylthieno[2,3-*b*]pyridine-3-carboxylic acid

Oxone (14.5 g, 24.0 mmol) dissolved in water (25 mL) was added to a rapidly stirred mixture of Intermediate 5 (10.6 g, 47 mmol) in MeOH (250 mL). The mixture was stirred at room temperature for 4 h. The reaction mixture was separated between DCM (300 mL) and water (200 mL). The organic layer was dried (Na₂SO₄) and concentrated *in vacuo* to give the *title compound* as a white crystalline solid (10.0 g, 88%). δ_H (DMSO- d_6) 14.20-13.80 (1H, br s), 8.73 (1H, dd, J 1.7, 8.3 Hz), 8.69 (1H, J 1.7, 4.6 Hz), 7.61 (1H, dd, J 4.6, 8.3 Hz), 3.05 (3H, s).

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INTERMEDIATE 7

2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylic acid

To a stirred solution of 2-fluoro-4-iodoaniline (6.0 g, 25 mmol) in THF (100 mL) at 0°C (ice bath) was added LiHMDS (1.0 M solution in THF, 20.0 mL, 20.0 mmol) slowly. The mixture was allowed to stir at room temperature for 30 minutes before cooling to 0°C and Intermediate 6 (2.0 g, 8.3 mmol) was added portionwise. The mixture was stirred at room temperature for 1 hour. After this time the reaction mixture was

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2X

poured onto ice and when at ambient temperature citric acid was added until a precipitate formed. The mixture was filtered to give the *title compound* as a pale brown crystalline solid (2.9 g, 84%). δ_{H} (DMSO- d_6) 14.00-13.00 (1H, br s), 10.80 (1H, s), 8.36 (1H, dd, J 1.3, 8.1 Hz), 8.32 (1H, dd, J 1.3, 4.8 Hz), 7.84 (1H, dd, J 1.8, 10.1 Hz), 7.69 (1H, d, J 8.3 Hz), 7.54 (1H, m), 7.42 (1H, dd, J 8.3, 4.8 Hz).

INTERMEDIATE 8

4-Iodo-1-isothiocyanato-2-methylbenzene

10 To a stirring solution of 4-iodo-2-methylaniline (1.0 g, 4.2 mmol) in DCM (50 mL) was added water (20 mL) followed by thiophosgene (490 mg, 4.2 mmol). The reaction mixture was stirred overnight before the layers were separated and the organic layer dried (Na_2SO_4) and evaporated *in vacuo* to give the desired product as a brown solid (1.05 g, 89%). δ_{H} (CDCl_3) 7.75 (1H, d, J 1.2 Hz), 7.62 (1H, dd, J 1.2, 8.3 Hz), 7.15 (1H, d, J 8.3 Hz), 2.20 (3H, s).

INTERMEDIATE 9

2-Chloro-4-iodo-1-isothiocyanatobenzene

20 To a stirred solution of 2-chloro-4-iodoaniline (1.0 g, 3.9 mmol) in DCM (50 mL) was added water (20 mL) followed by thiophosgene (476 mg, 4.1 mmol). The reaction mixture was stirred overnight before the layers were separated and the organic layer dried (Na_2SO_4) and evaporated *in vacuo* to give the desired product as a brown solid (1.0 g, 86%). δ_{H} (CDCl_3) 7.79 (1H, d, J 1.9 Hz), 7.58 (1H, dd, J 1.9, 8.4 Hz), 6.97 (1H, d, J 8.4 Hz).

INTERMEDIATE 10

30 (2R)-2-[(2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carbonyl)amino)-methyl]pyrrolidine-1-carboxylic acid *tert*-butyl ester

1-(3-Dimethylaminopropyl)-3-carbodiimide hydrochloride (139 mg, 0.72 mmol) was added to a solution of Intermediate 7 (150 mg, 0.36 mmol), 1-hydroxybenzotriazole (98 mg, 0.72 mmol), *N*-methylmorpholine (0.11 mL, 0.99 mmol) and (*R*)-2-

(aminomethyl)-1-BOC-pyrrolidine (144 mg, 0.72 mmol) in *N,N*-dimethylformamide (5 mL). The reaction mixture was stirred at r.t. for 20 h, then poured into EtOAc (25 mL). The organic solution was washed with sat. brine (3 x 25 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give a brown solid. The crude product was subjected to column chromatography (SiO₂, 4:1 hexanes/EtOAc) to give the *title compound*, which was evaporated from ether to give a hard foam (135 mg, 63%). δ_{H} (CDCl₃) 11.67 (1H, s), 8.35-8.33 (2H, m), 8.04 (1H, br s), 7.54-7.43 (3H, m), 7.32-7.30 (1H, m), 4.19 (1H, m), 3.82-3.78 (1H, m), 3.53-3.35 (3H, m), 2.18-1.86 (3H, m), 1.78 (1H, m), 1.45 (9H, s).

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INTERMEDIATE 11

(2*S*)-2-[(2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carbonyl)amino)-methyl]pyrrolidine-1-carboxylic acid *tert*-butyl ester

Prepared from Intermediate 7 (150 mg, 0.36 mmol), 1-hydroxybenzotriazole (98 mg, 0.72 mmol), *N*-methylmorpholine (0.11 mL, 0.99 mmol), 1-(3-dimethylamino-propyl)-3-carbodiimide hydrochloride (139 mg, 0.72 mmol) and (*S*)-2-(aminomethyl)-1-BOC-pyrrolidine (144 mg, 0.72 mmol) by the method of Intermediate 10. The *title compound* was evaporated from ether to give a colourless hard foam (139 mg, 64%). δ_{H} (CDCl₃) 11.67 (1H, s), 8.35-8.33 (2H, m), 8.04 (1H, br s), 7.54-7.43 (3H, m), 7.32-7.30 (1H, m), 4.19 (1H, m), 3.82-3.78 (1H, m), 3.53-3.35 (3H, m), 2.18-1.86 (3H, m), 1.78 (1H, m), 1.45 (9H, s).

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INTERMEDIATE 12

25 (2-Chloropyridin-3-yl)acetic acid

2-Chloro-3-(cyanomethyl)pyridine (D. H. Bremner *et al.*, *Synthesis*, 1997, 949) (10.3 g, 67.1 mmol) in conc. HCl (100 mL) was heated at reflux for 3 h. The reaction mixture was concentrated *in vacuo* and the residue suspended in water. The white solid was collected by filtration and washed with water, then dried *in vacuo* yielding the required product (11.15 g). δ_{H} (DMSO-*d*₆) 12.60 (1H, br s), 8.32 (1H, dd, *J* 4.7, 1.9 Hz), 7.86 (1H, dd, *J* 7.5, 1.9 Hz), 7.40 (1H, dd, *J* 7.5, 4.7 Hz), 3.75 (2H, s). LCMS (ES⁺) RT 1.85 minutes, 174 (M+H)⁺.

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INTERMEDIATE 13(2-Chloropyridin-3-yl)acetic acid methyl ester

To a suspension of Intermediate 12 (3.88 g, 22.6 mmol) in methanol was added
5 acetyl chloride (1.8 mL, 24.9 mmol) and the mixture heated at 70°C for 18 hours. The
solvents were removed *in vacuo* to give the *title compound* as a pale brown oil (4.63 g,
quant). δ_H (DMSO- d_6) 8.35 (1H, dd, J 4.7, 1.9 Hz), 7.88 (1H, dd, J 8.5, 1.9 Hz), 7.43
(1H, dd, J 8.5, 4.7 Hz), 3.80 (2H, s), 3.65 (3H, s). LCMS (ES⁺) RT 2.40 minutes, 186
(M+H)⁺.

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INTERMEDIATE 142-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylic acid methyl ester

To a solution of Intermediate 13 (4.1 g, 22.1 mmol) and Intermediate 1 (6.16 g,
15 22.1 mmol) in dry DMSO under nitrogen was added sodium hydride (1.05 g, 24.3 mmol,
60 wt % dispersion in mineral oil). The mixture was stirred at room temperature for 15
minutes then heated to 90°C for 3 hours. The reaction was cooled, then poured onto iced
water (200 mL). The aqueous phase was extracted with EtOAc (3 x 200 mL), the
combined organics washed with brine, dried (MgSO₄), filtered and the solvents removed
20 *in vacuo*. The sticky yellow solid was triturated with ethanol to give a fine yellow solid
which was collected by filtration, washed with diethyl ether and dried under suction to
give the *title compound* as a pale yellow solid (1.73 g). δ_H (DMSO- d_6) 10.30 (1H, s),
8.36-8.31 (2H, m), 7.87 (1H, dd, J 1.9, 10.0 Hz), 7.70 (1H, d, J 6.6 Hz), 7.51 (1H, t, J 8.5
Hz), 7.42 (1H, dd, J 5.7, 8.1 Hz), 3.94 (3H, s). LCMS (ES⁺) RT 4.00 minutes, 429
25 (M+H)⁺.

INTERMEDIATE 152-(2-Chloropyridin-3-yl)-*N*-methoxy-*N*-methylacetamide

30 Intermediate 12 (500 mg, 2.9 mmol) in dichloromethane (20 mL) with *N,O*-
dimethylhydroxylamine (300 mg, 3.04 mmol), EDC (583 mg, 3.04 mmol) and *N*-methyl-
morpholine (0.98 mL, 8.70 mmol) were stirred at r.t. for 18 h. The reaction mixture was
washed with 2M HCl, and the organic phase was dried (magnesium sulphate) and

concentrated *in vacuo*. Chromatography (SiO₂; 1:1 ethyl acetate:DCM) yielded the *title compound* (320 mg) as a white solid. δ_{H} (DMSO-d₆) 8.31 (1H, dd, *J* 4.7, 1.9 Hz), 7.81 (1H, dd, *J* 7.5, 1.9 Hz), 7.40 (1H, dd, *J* 7.5, 4.7 Hz), 3.93 (2H, s), 3.76 (3H, s), 3.15 (3H, s). LCMS (ES⁺) RT 2.22 minutes, 215/217 (M+H)⁺.

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INTERMEDIATE 16

2-(2-Chloro-1-oxypyridin-3-yl)-N-methoxy-N-methylacetamide

Intermediate 15 (270 mg, 1.25 mmol) was dissolved in DCM (5 mL) and treated with mCPBA (324 mg, 1.88 mmol). After stirring at r.t. for 3 days the reaction mixture was poured directly onto a flash column and chromatographed (SiO₂; ethyl acetate → 5% methanol in ethyl acetate), yielding the required product (265 mg) as a white solid. δ_{H} (DMSO-d₆) 8.39 (1H, dd, *J* 5.4, 2.5 Hz), 7.37-7.35 (2H, m), 3.98 (2H, s), 3.76 (3H, s), 3.15 (3H, s). LCMS(ES⁺) RT 1.81 minutes, 231/233 (M+H)⁺.

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EXAMPLE 1

Ethyl 2-[(2-fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylate

Sodium hydride (650 mg of a 60% dispersion in mineral oil, 16.2 mmol) was added portionwise over 10 min to a mixture of Intermediate 1 (3.75 g, 13.5 mmol) and ethyl (2-chloropyridin-3-yl)acetate (D. H. Bremner *et al.*, *Synthesis*, 1997, 949) (2.7 g, 13.5 mmol) in DMSO (25 mL). When gas evolution had slowed the mixture was heated at 70°C for 3 h then left at r.t. overnight. Water (150 mL) was added and the liquid decanted off from the resulting solid. The solid mass was treated with ethanol (40 mL) to give a fine white suspension which was filtered off, washed with ethanol (10 mL) and ether (2 x 15 mL) and dried *in vacuo* at 40°C to give the *title compound* as a white solid (2.90 g, 48%). δ_{H} (DMSO-d₆) 10.40 (1H, s), 8.40-8.30 (2H, m), 7.85 (1H, dd, *J* 1.9, 10.1 Hz), 7.70 (1H, d, *J* 8.5 Hz), 7.55-7.49 (1H, m), 7.43 (1H, dd, *J* 4.9, 8.0 Hz), 4.43 (2H, q, *J* 7.9 Hz), 1.41 (3H, t, *J* 7.9 Hz). LCMS (ES⁺) RT 5.27 minutes, 443 (M+H)⁺.

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EXAMPLE 2

2-[(2-Fluoro-4-iodophenyl)amino]-N-methylthieno[2,3-*b*]pyridine-3-carboxamide

Trimethylaluminium (1.5 mL of a 2M solution in hexane, 3.0 mmol) was added to a solution of methylamine (1.5 mL of a 2M solution in THF, 3.0 mmol) in toluene (5 mL). After 5 min Example 1 (250 mg, 0.60 mmol) was added and the mixture heated at 100°C for 4 h. After cooling the reaction was quenched with sat. ammonium chloride solution (75 mL) and HCl (10 mL, 2M) then extracted with EtOAc (80 mL). The organic phase was dried (Na₂SO₄) and concentrated *in vacuo* to give a solid. Trituration with ether (30 mL) and filtration gave the *title compound* as an off-white solid (138 mg, 57%). δ_{H} (CDCl₃) 11.13 (1H, br s), 8.25 (1H, dd, *J* 1.4, 4.7 Hz), 7.80 (1H, dd, *J* 1.4, 8.2 Hz), 7.46-7.42 (2H, m), 7.33 (1H, dd, *J* 8.3, 8.3 Hz), 7.21 (1H, dd, *J* 4.7, 8.2 Hz), 5.82 (1H, br s), 3.00 (3H, d, *J* 4.8 Hz). LCMS (ES⁻) RT 3.63 minutes, 426 (M-H)⁻.

EXAMPLE 3

2-[2-Fluoro-4-iodophenyl]amino]-N,N-dimethylthieno[2,3-*b*]pyridine-3-carboxamide
Prepared from Example 1 (100 mg, 0.23 mmol) and dimethylamine (0.35 mL of 2.0M solution in THF, 0.7 mmol) by the method of Example 2. *Title compound* obtained as a white solid (21 mg, 20%). δ_{H} (DMSO-*d*₆) 9.12 (1H, s), 8.35 (1H, dd, *J* 1.6, 4.7 Hz), 7.77 (1H, dd, *J* 1.6, 8.1 Hz), 7.67 (1H, dd, *J* 1.9, 10.6 Hz), 7.48 (1H, dd, *J* 1.1, 1.9 Hz), 7.35 (1H, dd, *J* 4.7, 8.0 Hz), 7.15-7.10 (1H, m), 2.87 (6H, s). LCMS (ES⁺) RT 3.29 minutes, 442 (M+H)⁺.

EXAMPLE 4

N-(2-Fluoro-4-iodophenyl)-3-(morpholin-4-ylcarbonyl)thieno[2,3-*b*]pyridin-2-amine
Prepared from Example 1 (250 mg, 0.60 mmol) and morpholine (0.26 mL, 3 mmol) by the method of Example 2. *Title compound* obtained as a white solid (215 mg, 78%). δ_{H} (DMSO-*d*₆) 9.22 (1H, br s), 8.34 (1H, dd, *J* 1.4, 4.6 Hz), 7.81 (1H, dd, *J* 1.4, 8.0 Hz), 7.68 (1H, dd, *J* 1.9, 10.5 Hz), 7.50-7.46 (1H, m), 7.35 (1H, dd, *J* 4.6, 8.0 Hz), 7.13 (1H, dd, *J* 8.6, 8.6 Hz), 3.54-3.48 (4H, m), 3.43-3.39 (4H, m). LCMS (ES⁺) RT 3.17 minutes, 484 (M+H)⁺.

EXAMPLE 5

N-(2-Fluoro-4-iodophenyl)-3-[(4-methylpiperazin-1-yl)carbonyl]thieno[2,3-b]pyridin-2-amine

Trimethylaluminium (1.5 mL of a 2M solution in hexane, 3.0 mmol) was added to a solution of 1-methylpiperazine (0.333 mL, 3.0 mmol) in toluene (5 mL). After 10 min

5 Example 1 (250 mg, 0.60 mmol) and toluene (2 mL) were added and the mixture heated at 90°C for 6 h. After cooling the mixture was quenched with NaOH (50 mL, 1M) and extracted with EtOAc (50 mL plus 25 mL). The combined organic extracts were washed with sat. brine (50 mL), dried (Na₂SO₄) and concentrated *in vacuo* to give a yellow solid. Trituration with hexane/ether (10:1, 30 mL) and filtration gave the *title compound* as a

10 pale yellow solid (245 mg, 87%). δ_{H} (DMSO-d₆) 9.13 (1H, br s), 8.37 (1H, br d, *J* 4.4 Hz), 7.79 (1H, br d, *J* 7.8 Hz), 7.67 (1H, br d, *J* 10.4 Hz), 7.47 (1H, br d, *J* 8.4 Hz), 7.37 (1H, dd, *J* 4.7, 8.1 Hz), 7.10 (1H, m), 3.30 (4H, br s), 2.21 (4H, br s), 2.14 (3H, s). LCMS (ES⁺) RT 2.09 minutes, 497 (M+H)⁺.

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EXAMPLE 6

2-[(4-Bromo-2-fluorophenyl)amino]-N-(2,3-dihydroxypropyl)thieno[2,3-b]pyridine-3-carboxamide

Trimethylaluminium (0.95 mL of a 2M solution in hexane, 1.90 mmol) was added

20 to a solution of 2,2-dimethyl-1,3-dioxolane-4-methanamine (249 mg, 1.9 mmol) in toluene (4 mL). After 2 minutes Intermediate 2 (150 mg, 0.38 mmol) was added and the mixture heated at 90°C for 4 h. After cooling the reaction was quenched with sat. ammonium chloride solution (5 mL) and HCl (5 mL, 2M), stirred, then extracted with EtOAc (2 x 25 mL) and DCM (25 mL). The organic phase was dried (Na₂SO₄) and

25 concentrated *in vacuo* to give a solid. Trituration with ether/hexane (1:3, 10 mL) and filtration gave the *title compound* as a white solid (95 mg, 57%). δ_{H} (DMSO-d₆) 10.64 (1H, br s), 8.36 (1H, dd, *J* 1.4, 4.7 Hz), 8.20 (1H, dd, *J* 1.4, 8.2 Hz), 7.89 (1H, dd, *J* 8.8, 8.8 Hz), 7.69 (1H, dd, *J* 2.1, 10.6 Hz), 7.58 (1H, dd, *J* 8.8, 8.8 Hz), 7.48-7.41 (2H, m), 4.86 (1H, d, *J* 5.0 Hz), 4.64 (1H, t, *J* 5.7 Hz), 3.72-3.66 (1H, m), 3.52-3.36 (3H, m), 3.31-

30 3.22 (1H, m). LCMS (ES⁺) RT 2.80 minutes, 440 (M(⁷⁹Br)+H)⁺.

EXAMPLE 7

2-[(2-Fluoro-4-iodophenyl)amino]-N-(2,3-dihydroxypropyl)thieno[2,3-*b*]pyridine-3-carboxamide

Prepared from Example 1 (150 mg, 0.34 mmol) and 2,2-dimethyl-1,3-dioxolane-4-methanamine (0.14 mL, 1.0 mmol) by the method of Example 6. *Title compound*

- 5 obtained as a pale-yellow solid (94 mg, 57%). δ_H (DMSO- d_6) 10.68 (1H, s), 8.36-8.35 (1H, m), 8.20 (1H, dd, *J* 1.2, 8.2 Hz), 7.90-7.87 (1H, m), 7.76 (1H, dd, *J* 1.7, 10.4 Hz), 7.62-7.59 (1H, m), 7.45-7.40 (2H, m), 4.86 (1H, d, *J* 5.0 Hz), 4.64 (1H, t, *J* 5.7 Hz), 3.72-3.64 (1H, m), 3.51-3.41 (3H, m), 3.40-3.34 (1H, m). LCMS (ES⁺) RT 2.91 minutes, 488 (M+H)⁺.

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EXAMPLE 8

Ethyl 2-[(2-fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylate 7-oxide

- Prepared from Intermediate 1 (2.38 g, 8.58 mmol) and ethyl (2-chloro-1-oxidopyridin-3-yl)acetate (D. H. Bremner *et al.*, *Synthesis*, 1997, 949) (1.85 g, 8.58 mmol) by the method of Example 1. *Title compound* obtained as a pale yellow solid (3.10 g, 79%). δ_H (DMSO- d_6) 10.31 (1H, br s), 8.20 (1H, d, *J* 5.9 Hz), 7.94 (1H, d, *J* 7.8 Hz), 7.89 (1H, dd, *J* 1.8, 10.0 Hz), 7.72 (1H, d, *J* 8.4 Hz), 7.55-7.46 (2H, m), 4.41 (2H, q, *J* 8.4 Hz), 1.40 (3H, t, *J* 7.1 Hz). LCMS (ES⁺) RT 3.44 minutes, 459 (M+H)⁺.

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EXAMPLE 9

N-(2,3-Dihydroxypropyl)-2-[(2-fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxamide 7-oxide

- 25 Prepared from Example 8 (200 mg, 0.43 mmol) and 2,2-dimethyl-1,3-dioxolane-4-methanamine (0.18 mL, 1.3 mmol) by the method of Example 6. *Title compound* obtained as a white solid (32 mg, 15%). δ_H (DMSO- d_6) 10.60 (1H, s), 8.22 (1H, m), 7.90 (1H, s), 7.84-7.76 (2H, m), 7.64-7.60 (1H, m), 7.45-7.40 (2H, m), 4.78 (1H, d, *J* 4.9 Hz), 4.64 (1H, t, *J* 5.6 Hz), 3.70-3.60 (1H, m), 3.50-3.15 (4H, m). LCMS (ES⁻) RT 2.37 minutes, 502 (M-H)⁻.

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EXAMPLE 10

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2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-b]pyridine-3-carbonitrile

To a solution of (2-chloropyridin-3-yl)acetonitrile (D. H. Bremner *et al.*, *Synthesis*, 1997, 949) (700 mg, 4.59 mmol) and Intermediate 1 (1.28 g, 4.60 mmol) in dry DMSO (15 mL) was added sodium hydride (202 mg, 60% in mineral oil, 5.06 mmol).

- 5 The mixture was stirred at room temperature for 15 minutes before heating to 90°C for four hours. The reaction mixture was poured into water (80 mL) and the solid precipitate filtered and washed with water/ethanol (2:1 mixture, 50 mL) followed by diethyl ether/hexane (1:1 mixture, 20 mL). The solid was dried in a vacuum oven and recrystallised from ethanol/water to give the *title compound* as a pale brown solid (800 mg, 45%). δ_{H}
- 10 (DMSO- d_6) 10.40 (1H, s), 8.37 (1H, dd, J 1.3, 4.6 Hz), 7.83-7.81 (2H, m), 7.64 (1H, d, J 8.3 Hz), 7.44 (1H, dd, J 4.7, 8.0 Hz), 7.33 (1H, dd, J 8.3, 8.3 Hz). LCMS RT 3.08 minutes, (ES⁻) 394 (M-H)⁻, (ES⁺) 396 (M+H)⁺.

EXAMPLE 11

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2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-b]pyridine-3-carboxylic acid amide

- A solution of Example 1 (250 mg, 0.56 mmol) in ethanol (5 mL) was added to liquid ammonia (15 mL) and the mixture heated in a Parr apparatus to 95°C at 800 psi for 18 hours. The volatiles were removed *in vacuo* to give an oily brown residue. Repeated
- 20 trituration with ethanol and DCM afforded the *title compound* as a white solid (18 mg). δ_{H} (DMSO- d_6) 11.20 (1H, bs), 8.34 (1H, d, J 3.4 Hz), 8.20 (1H, dd, J 8.2, 1.3 Hz), 7.76 (1H, dd, J 10.4, 1.8 Hz), 7.62 (1H, d, J 8.2 Hz), 7.57 (2H, br s), 7.49-7.39 (2H, m). LCMS (ES⁺) RT 3.11 minutes, 412 (M+H)⁺.

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EXAMPLE 12

- 2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-b]pyridin-3-yl[(pyrrolidin-1-yl)methanone
- Prepared from Example 1 (250 mg, 0.60 mmol) and pyrrolidine (0.25 mL, 3 mmol) by the method of Example 2. *Title compound* obtained as a pale yellow solid (136
- 30 mg, 51%). δ_{H} (DMSO- d_6) 9.21 (1H, br s), 8.35 (1H, dd, J 1.6, 4.7 Hz), 7.81 (1H, dd, J 1.6, 8.1 Hz), 7.67 (1H, dd, J 1.9, 10.5 Hz), 7.50-7.46 (1H, m), 7.35 (1H, dd, J 4.7, 8.1 Hz), 7.13 (1H, dd, J 8.6, 8.6 Hz), 3.32-3.30 (4H, m), 1.78-1.73 (4H, m). LCMS (ES⁺) RT 3.32 minutes, 468 (M+H)⁺.

EXAMPLE 135 2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylic acid (3-hydroxy-propyl)amide

Example 1 (500 mg, 1.13 mmol) was dissolved in dry toluene (6 mL) under nitrogen. To this solution was added trimethylaluminium (2.83 mL of a 2M solution in hexane, 5.66 mmol) over 5 minutes. After 10 minutes a solution of Intermediate 3 (1.07 g, 5.66 mmol) in dry toluene (5 mL) was added and the reaction heated to 100°C for 6
10 hours. The reaction was allowed to cool to room temperature and treated with 2M HCl (10 mL) and water (30 mL). The mixture was extracted with ethyl acetate (3 x 50 mL), then the organic phases were dried over Na₂SO₄ and filtered and the solvents removed *in vacuo*. The crude residue was dissolved in methanol (30 mL), treated with 2M HCl (20 mL) and stirred at ambient temperature for 18 hours. The mixture was concentrated *in*
15 *vacuo*, treated with 2M NaOH (20 mL) and extracted with ethyl acetate (3 x 50 mL). The organic phases were dried over Na₂SO₄, filtered, and the volatiles removed *in vacuo*. The residual solid was triturated with diethyl ether (10 mL) and dried in a vacuum oven to give the *title compound* as a pale yellow solid (100 mg, 19%). δ_H (DMSO-*d*₆) 10.75 (1H, br s), 8.35 (1H, m), 8.17 (1H, d, *J* 7.9 Hz), 8.01 (1H, br s), 7.75 (1H, d, *J* 10.1 Hz), 7.59
20 (1H, d, *J* 8.1 Hz), 7.44-7.41 (2H, m), 4.55 (1H, t, *J* 5.1 Hz), 3.54-3.48 (2H, m), 3.41-3.34 (2H, m), 1.75-1.67 (2H, m). LCMS (ES⁺) RT 3.22 minutes, 472 (M+H)⁺.

EXAMPLE 1425 2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylic acid (2(*S*),3-dihydroxypropyl)amide

Prepared from Example 1 (1.0 g, 2.26 mmol) and (*S*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methylamine (1.48 g, 11.3 mmol) by the method of Example 6. *Title compound* obtained as a white solid (425 mg, 39%). δ_H (DMSO-*d*₆) 10.67 (1H, bs), 8.36 (1H, d, *J*
30 3.8 Hz), 8.20 (1H, d, *J* 8.5 Hz), 7.88 (1H, bs), 7.76 (1H, d, *J* 10.5 Hz), 7.61 (1H, d, *J* 8.5 Hz), 7.46-7.40 (2H, m), 4.86 (1H, d, *J* 5.0 Hz), 4.64 (1H, t, *J* 5.7 Hz), 3.72-3.67 (1H, m), 3.52-3.38 (3H, m), 3.30-3.22 (1H, m). LCMS (ES⁺) RT 2.91 minutes, 488 (M+H)⁺.

EXAMPLE 15**2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylic acid (2*R*),3-dihydroxypropyl)amide**

- 5 Prepared from Example 1 (500 mg, 1.13 mmol) and (*R*)-(2,2-dimethyl-1,3-dioxolan-4-yl)methylamine (655 g, 4.52 mmol) by the method of Example 6. *Title compound* obtained as a white solid (100 mg, 18%). δ_{H} (DMSO- d_6) 10.67 (1H, bs), 8.36 (1H, d, *J* 3.8 Hz), 8.20 (1H, d, *J* 8.5 Hz), 7.88 (1H, bs), 7.76 (1H, d, *J* 10.5 Hz), 7.61 (1H, d, *J* 8.5 Hz), 7.46-7.40 (2H, m), 4.86 (1H, d, *J* 5.0 Hz), 4.64 (1H, t, *J* 5.7 Hz), 3.72-3.67 (1H, m), 3.52-3.38 (3H, m), 3.30-3.22 (1H, m). LCMS (ES^+) RT 2.91 minutes, 488 ($\text{M}+\text{H}$) $^+$.
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EXAMPLE 16

- 15 **2-[(4-Bromo-2-fluorophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylic acid methylamide**

- Prepared from Intermediate 2 (150 mg, 0.38 mmol) and a 2M solution of methylamine in THF (0.95 mL, 1.9 mmol) by the method of Example 2. *Title compound* obtained as a white solid (125 mg, 87%). δ_{H} (DMSO- d_6) 10.83 (1H, bs), 8.35 (1H, dd, *J* 1.4, 4.6 Hz), 8.18 (1H, dd, *J* 1.4, 8.2 Hz), 7.92 (1H, bs), 7.69 (1H, dd, *J* 2.1, 10.6 Hz), 7.59 (1H, dd, *J* 8.8, 8.8 Hz), 7.48-7.43 (1H, m), 7.42 (1H, dd, *J* 8.2, 4.6 Hz), 2.83 (3H, d, *J* 4.5 Hz). LCMS (ES^+) RT 3.45 minutes, 380/382 [$\text{Br}^{79}/\text{Br}^{81}$] ($\text{M}+\text{H}$) $^+$.
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EXAMPLE 17

- 25 **2-[(4-Iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylic acid ethyl ester**

- Prepared from ethyl (2-chloropyridin-3-yl)acetate (D. H. Bremner *et al.*, *Synthesis*, 1997, 949) (750 mg, 3.8 mmol) and 4-iodophenyl isothiocyanate (1.0 g, 3.8 mmol) by the method of Example 1. *Title compound* obtained as an off-white solid (800 mg, 50%). δ_{H} (DMSO- d_6) 10.34 (1H, br s), 8.33-8.30 (2H, m), 7.79 (2H, dt, *J* 2.0, 6.7 Hz), 7.43-7.31 (3H, m), 4.40 (2H, q, *J* 7.1 Hz), 1.40 (3H, t, *J* 7.1 Hz). LCMS (ES^+) RT 4.31 minutes, 425 ($\text{M}+\text{H}$) $^+$.
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EXAMPLE 18**2-[(4-Iodo-2-methylphenyl)amino]thieno[2,3-*b*]pyridine-3-carbonitrile**

To a stirred solution of Intermediate 8 (429 mg, 3.28 mmol) and (2-chloropyridin-3-yl)acetonitrile (D. H. Bremner *et al.*, *Synthesis*, 1997, 949) (500 mg, 3.28 mmol) in DMSO (20 mL) was added sodium hydride (164 mg, 4.1 mmol). When evolution of gases had finished the reaction mixture was heated for 3 hours at 80°C. After this time the reaction mixture was poured onto ice and extracted into DCM (2 x 50 mL). The organics were dried (Na₂SO₄) and then evaporated *in vacuo* to give a brown residue. Column chromatography (SiO₂, 5:1 hexane:EtOAc) gave the *title compound* as a yellow powder (198 mg, 15%). ¹H (DMSO-*d*₆) 10.11 (1H, s), 8.29 (1H, dd, *J* 1.5, 4.7 Hz), 7.75 (2H, m), 7.63 (1H, dd, *J* 1.7, 8.1 Hz), 7.39 (1H, dd, *J* 8.1, 4.8 Hz), 7.19 (1H, d, *J* 8.3 Hz), 2.24 (3H, s). LCMS (ES⁺) RT 3.68 minutes, 392 (M+H)⁺.

EXAMPLE 19**2-[(4-Bromo-2-fluorophenyl)amino]thieno[2,3-*b*]pyridine-3-carbonitrile**

4-Bromo-2-fluoro-1-isothiocyanatobenzene (250 mg, 1.08 mmol) and (2-chloropyridin-3-yl)acetonitrile (D. H. Bremner *et al.*, *Synthesis*, 1997, 949) (165 mg, 1.08 mmol) were stirred in DMSO (20 mL) and sodium hydride (52 mg, 1.3 mmol) added portionwise. After evolution of gases had finished the reaction mixture was heated for 4 h at 80°C. After this time the reaction mixture was added to ice (50 mL) and a precipitate formed. This was filtered and purified by preparative HPLC (pH 10, 2-3 min) to give the *title compound* as a white powder (30 mg, 9%). ¹H (DMSO-*d*₆) 10.45 (1H, s), 8.31 (1H, d, *J* 3.9 Hz), 7.75 (2H, m), 7.51-7.38 (3H, m). LCMS (ES⁺) RT 3.49 minutes, 350 (M+H)⁺.

EXAMPLE 20**2-[(2-Chloro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carbonitrile**

Intermediate 9 (300 mg, 1.01 mmol) and (2-chloropyridin-3-yl)acetonitrile (D. H. Bremner *et al.*, *Synthesis*, 1997, 949) (165 mg, 1.01 mmol) were stirred together in DMSO (20 mL) and sodium hydride (48 mg, 1.21 mmol) was added portionwise. After

evolution of gases was complete the reaction mixture was heated for 4 h at 80°C. After this time the reaction mixture was added to ice (50 mL) and then extracted into DCM (2 x 50 mL), which was dried (Na₂SO₄) and evaporated *in vacuo* to give a yellow residue. This residue was subjected to column chromatography (SiO₂, 1:4 EtOAc:hexane) to afford the *title compound* as a yellow powder (118 mg, 28%). δ_{H} (DMSO-d₆) 10.38 (1H, s), 8.35 (1H, dd, *J* 1.5, 4.8 Hz), 8.00 (1H, d, *J* 1.9 Hz), 7.80 (2H, m), 7.42 (1H, dd, *J* 8.0, 4.8 Hz), 7.35 (1H, d, *J* 8.3 Hz). LCMS (ES⁺) RT 3.70 minutes, 412 (M+H)⁺.

EXAMPLE 21

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2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylic acid (2-amino-2-methylpropyl)amide

Trimethylaluminium (2.85 mL of a 2M solution in hexane, 5.7 mmol) was added to a solution of 1,2-diamino-2-methylpropane (498 mg, 5.7 mmol) in toluene (5 mL). After 10 minutes Example 1 (500 mg, 1.13 mmol) was added and the mixture heated at 100°C for 4 h. After cooling the reaction was quenched with 10% sodium hydroxide solution (75 mL) and extracted with EtOAc (100 mL). The organic phase was dried (Na₂SO₄) and concentrated *in vacuo* to give a solid. Trituration with hexanes (30 mL) and filtration gave the *title compound* as a yellow solid (248 mg, 45%). δ_{H} (DMSO-d₆) 10.72 (1H, m), 8.43 (1H, dd, *J* 1.7, 8.0 Hz), 7.84 (1H, dd, *J* 1.7, 4.7 Hz), 7.80-7.40 (2H, s), 7.46-7.35 (2H, m), 7.21 (1H, m), 7.00 (1H, dd, *J* 4.7, 8.0 Hz), 3.40 (2H, d, *J* 5.7 Hz), 1.25 (6H, s). LCMS (ES⁺) RT 2.23 minutes, 501 (M+H)⁺.

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EXAMPLE 22

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2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylic acid [(4*R*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy]amide

1-(3-Dimethylaminopropyl)-3-carbodiimide hydrochloride (131 mg, 0.68 mmol) was added to a solution of Intermediate 7 (142 mg, 0.34 mmol), 1-hydroxybenzotriazole (93 mg, 0.68 mmol), *N*-methylmorpholine (0.10 mL, 0.94 mmol) and (4*R*)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxylamine (WO 02/006213) (101 mg, 0.68 mmol) in *N,N*-dimethylformamide (5 mL). The reaction mixture was stirred at r.t. for 20 h, then poured into EtOAc (25 mL). The organic solution was washed with sat. brine (2 x 25 mL), then

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dried (Na₂SO₄), filtered and concentrated *in vacuo* to give a brown solid. The crude product was subjected to column chromatography (SiO₂, 2:1 hexanes/EtOAc) to give the *title compound* as a pale yellow powder (135 mg, 95%). δ_{H} (DMSO-d₆) 10.98 (1H, s), 8.74 (1H, s), 8.28-8.26 (1H, m), 7.94-7.91 (1H, m), 7.48-7.46 (2H, m), 7.37-7.32 (1H, m), 7.23 (1H, dd, *J* 4.8, 8.2 Hz), 4.46-4.40 (1H, m), 4.17 (1H, dd, *J* 3.8, 11.7 Hz), 4.11-4.01 (2H, m), 3.79 (1H, dd, *J* 7.0, 8.3 Hz), 1.15 (3H, s), 1.10 (3H, s). LCMS RT 3.38 minutes, (ES⁻) 542 (M-H)⁻, (ES⁺) 544 (M+H)⁺.

EXAMPLE 23

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2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylic acid [(2*R*)-2,3-dihydroxypropoxy]amide

A solution of Example 22 (125 mg, 0.23 mmol) in methanol (5 mL) and THF (5 mL) was treated with 10% aq. HCl (5 mL). The reaction mixture was stirred for 3.5 h at r.t., then diluted with EtOAc (25 mL). The organic solution was washed with sat. brine (2 x 25 mL), then dried (Na₂SO₄), filtered and concentrated *in vacuo* to give the *title compound* as a white powder, which was washed with EtOAc, then hexanes, and dried under suction (76 mg, 66%). δ_{H} (DMSO-d₆) 11.31 (1H, s), 10.33 (1H, s), 8.34-8.33 (1H, m), 8.12-8.09 (1H, m), 7.79-7.76 (1H, m), 7.63-7.60 (1H, m), 7.45-7.40 (2H, m), 4.89-4.88 (1H, m), 4.62-4.59 (1H, m), 3.99-3.97 (1H, m), 3.85-3.80 (2H, m), 3.43 (2H, m). LCMS RT 3.38 minutes, (ES⁻) 502 (M-H)⁻, (ES⁺) 504 (M+H)⁺.

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EXAMPLE 24

(1-{2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carbonyl}piperidin-4-yl)-carbamic acid *tert*-butyl ester

Prepared from Intermediate 7 (150 mg, 0.36 mmol), 1-hydroxybenzotriazole (98 mg, 0.72 mmol), *N*-methylmorpholine (0.11 mL, 0.99 mmol), 1-(3-dimethylamino-propyl)-3-carbodiimide hydrochloride (139 mg, 0.72 mmol) and 4-(BOC-amino)-piperidine (145 mg, 0.72 mmol), by the method of Example 22. The *title compound* was evaporated from ether to give a colourless hard foam (111 mg, 51%). δ_{H} (CDCl₃, contains rotamers) 9.17 (0.64H, s), 8.90 (0.36H, s), 8.39-8.37 (1H, m), 7.75-7.73 (0.36H, m), 7.66-7.63 (0.64H, m), 7.53-7.50 (2H, m), 7.44-7.39 (1H, m), 7.31-7.28 (1H, m), 4.57

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(0.36H, m), 4.40 (0.64H, m), 4.20-4.15 (1.28H, m), 4.03-3.98 (0.72H, m), 3.72 (1H, m), 3.16-3.08 (2H, m), 2.05-2.00 (2H, m), 1.47 (3.2H, s), 1.44 (5.8H, s), 1.36-1.28 (2H, m). LCMS RT 3.36 minutes, (ES⁻) 595 (M-H)⁻, (ES⁺) 597 (M+H)⁺.

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EXAMPLE 25

2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylic acid (4-aminopiperidin-1-yl)amide dihydrochloride

A solution of Example 24 (99 mg, 0.17 mmol) in methanol (2 mL) was treated with 4M HCl in 1,4-dioxane (5 mL) and stirred at r.t. for 3 h. The reaction mixture was concentrated *in vacuo* to give a yellow gum, which was dissolved in water (25 mL). The aqueous solution was washed with ether (2 x 25 mL), and then evaporated *in vacuo*. The resulting gum was triturated with ether to give the *title compound* as a yellow powder (89 mg, 94%). δ_{H} (DMSO-*d*₆, contains rotamers) 9.24 (0.5H, s), 9.14 (0.5H, s), 8.38-8.37 (1H, m), 8.13 (3H, br s), 7.82-7.75 (1H, m), 7.72-7.66 (1H, m), 7.55-7.47 (1H, m), 7.38 (1H, dd, *J* 4.7, 8.1 Hz), 7.23-7.10 (1H, m), 4.02 (2H, br m), 3.25 (1H, br m), 3.06-2.98 (1H, m), 2.88-2.81 (1H, m), 1.93-1.89 (2H, m), 1.43 (2H, br m). LCMS RT 2.86 minutes, (ES⁺) 497 (M+H)⁺.

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EXAMPLE 26

2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylic acid (2-hydroxy-1-methylethyl)amide

Prepared from Intermediate 7 (150 mg, 0.36 mmol), 1-hydroxybenzotriazole (98 mg, 0.72 mmol), *N*-methylmorpholine (0.11 mL, 0.99 mmol), 1-(3-dimethylamino-propyl)-3-carbodiimide hydrochloride (139 mg, 0.72 mmol) and 2-aminopropanol (0.06 mL, 0.72 mmol), by the method of Example 22. The crude product was subjected to column chromatography (SiO₂, 1:1 hexanes/EtOAc) to give the *title compound*, which was recrystallised from EtOAc/hexanes to give a beige powder (56 mg, 33%). δ_{H} (DMSO-*d*₆) 10.45 (1H, s), 8.37-8.36 (1H, m), 8.16-8.13 (1H, m), 7.76-7.71 (2H, m), 7.60-7.57 (1H, m), 7.46-7.36 (2H, m), 4.78 (1H, t, *J* 5.6 Hz), 4.10-4.03 (1H, m), 3.52-3.35 (2H, m), 1.13 (3H, d, *J* 6.7 Hz). LCMS RT 3.46 minutes, (ES⁺) 472 (M+H)⁺.

EXAMPLE 273-[(2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carbonyl)amino)methyl]-azetidine-1-carboxylic acid *tert*-butyl ester

5 Prepared from Intermediate 7 (150 mg, 0.36 mmol), 1-hydroxybenzotriazole (98 mg, 0.72 mmol), *N*-methylmorpholine (0.11 mL, 0.99 mmol), 1-(3-dimethylamino-propyl)-3-carbodiimide hydrochloride (139 mg, 0.72 mmol) and 1-BOC-3-(aminomethyl)azetidine (135 mg, 0.72 mmol), by the method of Example 22. The crude product was subjected to column chromatography (SiO₂, 3:2 hexanes/EtOAc) to give the

10 *title compound*, which was recrystallised from ether/hexanes to give a cream-coloured powder (116 mg, 55%). δ_H (CDCl₃) 8.37 (1H, dd, *J* 1.3, 4.7 Hz), 7.84 (1H, dd, *J* 1.3, 8.2 Hz), 7.56-7.53 (2H, m), 7.46-7.41 (1H, m), 7.32 (1H, dd, *J* 4.7, 8.2 Hz), 6.08 (1H, m), 4.14-4.09 (2H, m), 3.77-3.73 (4H, m), 2.94-2.92 (1H, m), 1.46 (9H, s). LCMS RT 3.68 minutes, (ES⁻) 581 (M-H)⁻, (ES⁺) 583 (M+H)⁺.

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EXAMPLE 28(1-{2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carbonyl}azetidin-3-ylmethyl)carbamic acid *tert*-butyl ester

20 Prepared from Intermediate 7 (150 mg, 0.36 mmol), 1-hydroxybenzotriazole (98 mg, 0.72 mmol), *N*-methylmorpholine (0.11 mL, 0.99 mmol), 1-(3-dimethylamino-propyl)-3-carbodiimide hydrochloride (139 mg, 0.72 mmol) and 3-(BOC-aminomethyl)-azetidine (135 mg, 0.72 mmol), by the method of Example 22. The *title compound* was evaporated from ether to give a colourless hard foam (75 mg, 36%). δ_H (CDCl₃) 8.25

25 (1H, dd, *J* 1.5, 4.7 Hz), 7.67 (1H, dd, *J* 1.5, 8.1 Hz), 7.46-7.41 (2H, m), 7.38-7.33 (1H, m), 7.22 (1H, dd, *J* 4.7, 8.1 Hz), 4.59 (1H, br s), 4.15-4.09 (2H, m), 3.80-3.75 (2H, m), 3.32 (2H, m), 2.78-2.74 (1H, m), 1.35 (9H, s). LCMS RT 3.41 minutes, (ES⁻) 581 (M-H)⁻, (ES⁺) 583 (M+H)⁺.

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EXAMPLE 293-[(2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carbonyl)amino]azetidine-1-carboxylic acid *tert*-butyl ester

Prepared from Intermediate 7 (150 mg, 0.36 mmol), 1-hydroxybenzotriazole (98 mg, 0.72 mmol), *N*-methylmorpholine (0.11 mL, 0.99 mmol), 1-(3-dimethylamino-propyl)-3-carbodiimide hydrochloride (139 mg, 0.72 mmol) and 1-BOC-3-aminoazetidine (125 mg, 0.72 mmol), by the method of Example 22. The *title compound* was

- 5 recrystallised from ether/hexanes to give a cream-coloured powder (116 mg, 57%). δ_H (CDCl₃) 8.38 (1H, dd, *J* 1.2, 4.7 Hz), 7.90 (1H, dd, *J* 1.2, 8.1 Hz), 7.56-7.53 (2H, m), 7.45-7.40 (1H, m), 7.35 (1H, dd, *J* 4.7, 8.1 Hz), 6.19 (1H, d, *J* 6.9 Hz), 4.89-4.84 (1H, m), 4.44-4.38 (2H, m), 3.93-3.88 (2H, m), 1.48 (9H, s). LCMS RT 3.66 minutes, (ES⁻) 567 (M-H)⁻, (ES⁺) 569 (M+H)⁺.

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EXAMPLE 30

[3-(Aminomethyl)azetidin-1-yl]-{2-[(2-fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridin-3-yl}-methanone

- 15 A solution of Example 28 (65 mg, 0.11 mmol) in DCM (7 mL) was treated with trifluoroacetic acid (3 mL) and stirred for 1 h at r.t. The reaction mixture was concentrated *in vacuo* to give a yellow gum, which was dissolved in water (25 mL) and basified to pH 10 with sodium carbonate. The aqueous solution was extracted with 5% methanol in DCM (4 x 25 mL), and the extracts combined, then dried (Na₂SO₄), filtered
- 20 and concentrated *in vacuo*. The crude product was subjected to column chromatography (SiO₂, 4:1 DCM/methanol) to give the *title compound* as a gummy solid, which was triturated from ether to give a cream-coloured powder (34 mg, 63%). δ_H (DMSO-*d*₆) 8.31 (1H, m), 7.93 (1H, m), 7.72 (1H, dd, *J* 1.5, 10.5 Hz), 7.55 (1H, m), 7.37 (1H, dd, *J* 4.6, 8.1 Hz), 7.29-7.24 (1H, m), 4.88 (2H, br s), 4.03-3.97 (2H, m), 3.71-3.67 (2H, m), 2.65
- 25 (1H, m), 2.70-2.68 (2H, m). LCMS RT 2.93 minutes, (ES⁻) 481 (M-H)⁻, (ES⁺) 483 (M+H)⁺.

EXAMPLE 31

- 30 2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylic acid [(2*R*)-pyrrolidin-2-ylmethyl]amide

A solution of Intermediate 10 (135 mg, 0.23mmol) in methanol (2 ml) was treated with 4M HCl in 1,4-dioxane (5 mL) and stirred at r.t. for 30 min. The reaction mixture

was concentrated *in vacuo* to give a yellow gum, which was dissolved in water (25 mL). The aqueous solution was washed with ether (2 x 25 mL), then basified to pH 11 with 25% aq. ammonium hydroxide. The aqueous solution was extracted with DCM (2 x 25 mL), and the organic extracts combined, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was subjected to column chromatography (SiO₂, 91:8:1 DCM/methanol/25% aq. ammonium hydroxide) to give the *title compound*, which was freeze-dried overnight from acetonitrile/water to give a cream-coloured powder (73 mg, 65%). δ_{H} (DMSO-d₆) 10.63 (1H, s), 9.12 (1H, br s), 8.37 (1H, dd, *J* 1.7, 8.0 Hz), 7.84 (1H, dd, *J* 1.7, 4.7 Hz), 7.47 (1H, dd, *J* 2.0, 10.4 Hz), 7.42-7.38 (1H, m), 7.17-7.11 (1H, m), 7.00 (1H, dd, *J* 4.7, 8.0 Hz), 3.68-3.61 (1H, m), 3.51-3.49 (2H, m), 3.17-3.12 (2H, m), 2.28-1.62 (4H, m). LCMS RT 2.42 minutes, (ES⁻) 495 (M-H)⁻, (ES⁺) 497 (M+H)⁺.

EXAMPLE 32

15 2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylic acid [(2*S*)-pyrrolidin-2-ylmethyl]amide

Prepared from Intermediate 11 (139 mg, 0.23 mmol) by the method of Example 31. The *title compound* was obtained as a cream-coloured powder (81 mg, 70%). δ_{H} (DMSO-d₆) 10.63 (1H, s), 9.12 (1H, br s), 8.37 (1H, dd, *J* 1.7, 8.0 Hz), 7.84 (1H, dd, *J* 1.7, 4.7 Hz), 7.47 (1H, dd, *J* 2.0, 10.4 Hz), 7.42-7.38 (1H, m), 7.17-7.11 (1H, m), 7.00 (1H, dd, *J* 4.7, 8.0 Hz), 3.68-3.61 (1H, m), 3.51-3.49 (2H, m), 3.17-3.12 (2H, m), 2.28-1.62 (4H, m). LCMS RT 2.42 minutes, (ES⁻) 495 (M-H)⁻, (ES⁺) 497 (M+H)⁺.

EXAMPLE 33

25 (3*S*)-3-({2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carbonyl}amino)-piperidine-1-carboxylic acid *tert*-butyl ester

Prepared from Intermediate 7 (150 mg, 0.36 mmol), 1-hydroxybenzotriazole (98 mg, 0.72 mmol), *N*-methylemorpholine (0.11 mL, 0.99 mmol), 1-(3-dimethylamino-propyl)-3-carbodiimide hydrochloride (139 mg, 0.72 mmol) and (*S*)-1-BOC-3-aminopiperidine (145 mg, 0.72 mmol), by the method of Example 22. The *title compound* was obtained as a gummy yellow solid (131 mg, 61%). δ_{H} (CDCl₃) 11.34 (1H, s), 8.36-8.34 (1H, m), 7.90-7.88 (1H, m), 7.55-7.52 (2H, m), 7.45-7.42 (1H, m), 7.32-7.29

(1H, m), 5.32 (1H, br s), 4.31 (1H, m), 3.83-3.78 (2H, m), 3.46-3.42 (1H, m), 3.17 (1H, m), 1.89-1.73 (2H, m), 1.67 (2H, m), 1.47 (9H, s). LCMS RT 4.04 minutes, (ES⁺) 597 (M+H)⁺.

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EXAMPLE 34

(3R)-3-({2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-b]pyridine-3-carbonyl}amino)-piperidine-1-carboxylic acid tert-butyl ester

Prepared from Intermediate 7 (150 mg, 0.36 mmol), 1-hydroxybenzotriazole (98 mg, 0.72 mmol), *N*-methylmorpholine (0.11 mL, 0.99 mmol), 1-(3-dimethylamino-propyl)-3-carbodiimide hydrochloride (139 mg, 0.72 mmol) and (*R*)-1-BOC-3-aminopiperidine (145 mg, 0.72 mmol), by the method of Example 22. The *title compound* was obtained as a pale pink gummy solid (136 mg, 63%). δ_H (CDCl₃) 11.34 (1H, s), 8.36-8.34 (1H, m), 7.90-7.88 (1H, m), 7.55-7.52 (2H, m), 7.45-7.42 (1H, m), 7.32-7.29 (1H, m), 5.32 (1H, br s), 4.31 (1H, m), 3.83-3.78 (2H, m), 3.46-3.42 (1H, m), 3.17 (1H, m), 1.89-1.73 (2H, m), 1.67 (2H, m), 1.47 (9H, s). LCMS RT 4.03 minutes, (ES⁺) 597 (M+H)⁺.

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EXAMPLE 35

2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-b]pyridine-3-carboxylic acid [(3S)-piperidin-3-yl]amide dihydrochloride

A solution of Example 33 (120 mg, 0.20 mmol) in methanol (2 mL) was treated with 4M HCl in 1,4-dioxane (5 mL) and stirred at r.t. for 3 h. The reaction mixture was evaporated *in vacuo* to give the *title compound* as a gummy yellow solid, which was triturated from ether to give a yellow powder (112 mg, 98%). δ_H (DMSO-d₆) 10.38 (1H, s), 9.04-8.92 (2H, m), 8.38 (1H, dd, *J* 1.3, 4.6 Hz), 8.17-8.14 (2H, m), 7.75 (1H, dd, *J* 1.8, 10.4 Hz), 7.61-7.58 (1H, m), 7.44 (1H, dd, *J* 4.6, 8.2 Hz), 7.42-7.36 (1H, m), 4.09 (1H, m), 3.34-3.31 (1H, m), 3.21-3.17 (1H, m), 2.94-2.79 (2H, m), 1.91 (2H, m), 1.74-1.61 (2H, m). LCMS RT 2.38 minutes, (ES⁺) 497 (M+H)⁺.

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EXAMPLE 36

2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylic acid [(3*R*)-piperidin-3-yl]amide dihydrochloride

Prepared from Example 34 (126 mg, 0.21 mmol) by the method of Example 35.

The *title compound* was obtained as a yellow powder (115 mg, 96%). δ_{H} (DMSO- d_6)

5 10.38 (1H, s), 9.04-8.92 (2H, m), 8.38 (1H, dd, *J* 1.3, 4.6 Hz), 8.17-8.14 (2H, m), 7.75 (1H, dd, *J* 1.8, 10.4 Hz), 7.61-7.58 (1H, m), 7.44 (1H, dd, *J* 4.6, 8.2 Hz), 7.42-7.36 (1H, m), 4.09 (1H, m), 3.34-3.31 (1H, m), 3.21-3.17 (1H, m), 2.94-2.79 (2H, m), 1.91 (2H, m), 1.74-1.61 (2H, m). LCMS RT 2.38 minutes, (ES⁺) 497 (M+H)⁺.

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EXAMPLE 37

(1-{2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carbonyl}-(3*R*)-pyrrolidin-3-yl)carbamic acid *tert*-butyl ester

Prepared from Intermediate 7 (150 mg, 0.36 mmol), 1-hydroxybenzotriazole (98

15 mg, 0.72 mmol), *N*-methylmorpholine (0.11 mL, 0.99 mmol), 1-(3-dimethylamino-propyl)-3-carbodiimide hydrochloride (139 mg, 0.72 mmol) and (*R*)-3-(BOC-amino)-pyrrolidine (186 mg, 0.72 mmol), by the method of Example 22. The crude product was subjected to column chromatography (SiO₂, 3:2 hexanes/EtOAc) to give the *title compound*, which was evaporated from ether to give a colourless hard foam (110 mg, 20 52%). δ_{H} (CDCl₃) 9.03 (1H, s), 8.28 (1H, dd, *J* 1.5, 4.7 Hz), 7.56 (1H, dd, *J* 1.5, 8.1 Hz), 7.43-7.39 (2H, m), 7.34-7.29 (1H, m), 7.22-7.18 (1H, m), 4.50 (1H, br s), 4.16-4.14 (1H, m), 3.71 (1H, dd, *J* 6.2, 11.8 Hz), 3.63-3.56 (2H, m), 3.30 (1H, dd, *J* 5.1, 11.8 Hz), 2.19-2.12 (1H, m), 1.86-1.77 (1H, m), 1.35 (9H, s). LCMS RT 3.33 minutes, (ES⁻) 581 (M-H)⁻, (ES⁺) 583 (M+H)⁺.

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EXAMPLE 38

(1-{2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carbonyl}-(3*S*)-pyrrolidin-3-yl)carbamic acid *tert*-butyl ester

30 Prepared from Intermediate 7 (150 mg, 0.36 mmol), 1-hydroxybenzotriazole (98 mg, 0.72 mmol), *N*-methylmorpholine (0.11 mL, 0.99 mmol), 1-(3-dimethylamino-propyl)-3-carbodiimide hydrochloride (139 mg, 0.72 mmol) and (*S*)-3-(BOC-amino)-pyrrolidine (186 mg, 0.72 mmol), by the method of Example 37. The *title compound* was

obtained as a colourless hard foam (125 mg, 59%). δ_H (CDCl₃) 9.03 (1H, s), 8.28 (1H, dd, J 1.5, 4.7 Hz), 7.56 (1H, dd, J 1.5, 8.1 Hz), 7.43-7.39 (2H, m), 7.34-7.29 (1H, m), 7.22-7.18 (1H, m), 4.50 (1H, br s), 4.16-4.14 (1H, m), 3.71 (1H, dd, J 6.2, 11.8 Hz), 3.63-3.56 (2H, m), 3.30 (1H, dd, J 5.1, 11.8 Hz), 2.19-2.12 (1H, m), 1.86-1.77 (1H, m), 1.35 (9H, s). LCMS RT 3.33 minutes, (ES⁻) 581 (M-H)⁻, (ES⁺) 583 (M+H)⁺.

EXAMPLE 39

10 (1-{2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carbonyl}azetidin-3-yl)-carbamic acid *tert*-butyl ester

Prepared from Intermediate 7 (150 mg, 0.36 mmol), 1-hydroxybenzotriazole (98 mg, 0.72 mmol), *N*-methylmorpholine (0.11 mL, 0.99 mmol), 1-(3-dimethylamino-propyl)-3-carbodiimide hydrochloride (139 mg, 0.72 mmol) and 3-(BOC-amino)azetidine (125 mg, 0.72 mmol), by the method of Example 22. The crude product was subjected to
15 column chromatography (SiO₂, 3:1 hexanes/EtOAc) to give the *title compound*, which was evaporated from ether to a cream-coloured powder (100 mg, 49%). δ_H (CDCl₃) 10.11 (1H, s), 8.35 (1H, dd, J 1.5, 4.7 Hz), 7.76 (1H, dd, J 1.5, 8.1 Hz), 7.55-7.51 (2H, m), 7.47-7.41 (1H, m), 7.31 (1H, dd, J 4.7, 8.1 Hz), 4.95 (1H, br s), 4.52 (1H, br s), 4.46-4.40 (2H, m), 4.01-3.96 (2H, m), 1.45 (9H, s). LCMS RT 3.47 minutes, (ES⁻) 567
20 (M-H)⁻, (ES⁺) 569 (M+H)⁺.

EXAMPLE 40

25 4-{2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carbonyl}amino)-piperidine-1-carboxylic acid *tert*-butyl ester

Prepared from Intermediate 7 (150 mg, 0.36 mmol), 1-hydroxybenzotriazole (98 mg, 0.72 mmol), *N*-methylmorpholine (0.11 mL, 0.99 mmol), 1-(3-dimethylamino-propyl)-3-carbodiimide hydrochloride (139 mg, 0.72 mmol) and 4-amino-1-BOC-piperidine (145 mg, 0.72 mmol), by the method of Example 22. The crude product was
30 adsorbed onto SiO₂ and subjected to column chromatography (SiO₂, 2:1 hexanes/EtOAc) to give the *title compound*, which was evaporated from ether to give cream-coloured flakes (97 mg, 45%). δ_H (CDCl₃) 11.18 (1H, s), 8.36 (1H, dd, J 1.4, 4.7 Hz), 7.81 (1H, dd, J 1.4, 8.2 Hz), 7.55-7.53 (2H, m), 7.46-7.41 (1H, m), 7.32 (1H, dd, J 4.7, 8.2 Hz),

5.74 (1H, d, J 7.6 Hz), 4.27-4.20 (1H, m), 4.15-4.11 (2H, m), 3.03-2.96 (2H, m), 2.15-2.10 (2H, m), 1.50 (9H, s), 1.45 (2H, m). LCMS RT 3.95 minutes, (ES⁻) 567 (M-H)⁻, (ES⁺) 569 (M+H)⁺.

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EXAMPLE 41

[(3R)-3-Aminopyrrolidin-1-yl]-{2-[(2-fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridin-3-yl}-methanone

Prepared from Example 37 (100 mg, 0.17 mmol) following the method of

10 Example 35. The *title compound* was obtained as a yellow powder (100 mg, quant.). δ_H (DMSO- d_6) 9.29 (1H, s), 8.36 (1H, dd, J 1.5, 4.7 Hz), 8.29 (3H, s), 7.91-7.89 (1H, m), 7.72 (1H, dd, J 1.8, 10.4 Hz), 7.55-7.52 (1H, m), 7.37 (1H, dd, J 4.7, 8.1 Hz), 7.24-7.19 (1H, m), 3.79-3.72 (1H, m), 3.70-3.58 (2H, m), 3.51-3.38 (2H, m), 2.20-2.13 (1H, m), 2.01-1.97 (1H, m). LCMS RT 2.24 minutes, (ES⁻) 481 (M-H)⁻, (ES⁺) 483 (M+H)⁺.

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EXAMPLE 42

[(3S)-3-Aminopyrrolidin-1-yl]-{2-[(2-fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridin-3-yl}-methanone

20 Prepared from Example 38 (115 mg, 0.20 mmol) following the method of

Example 35. The *title compound* was obtained as a yellow powder (109 mg, 99%). δ_H (DMSO- d_6) 9.29 (1H, s), 8.36 (1H, dd, J 1.5, 4.7 Hz), 8.29 (3H, s), 7.91-7.89 (1H, m), 7.72 (1H, dd, J 1.8, 10.4 Hz), 7.55-7.52 (1H, m), 7.37 (1H, dd, J 4.7, 8.1 Hz), 7.24-7.19 (1H, m), 3.79-3.72 (1H, m), 3.70-3.58 (2H, m), 3.51-3.38 (2H, m), 2.20-2.13 (1H, m),
25 2.01-1.97 (1H, m). LCMS RT 2.24 minutes, (ES⁻) 481 (M-H)⁻, (ES⁺) 483 (M+H)⁺.

EXAMPLE 43

2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylic acid (piperidin-4-yl)amide

30

Prepared from Example 40 (87 mg, 0.15 mmol) following the method of Example

35. The *title compound* was obtained as a yellow powder (80 mg, 96%). δ_H (DMSO- d_6) 10.31 (1H, s), 8.84 (1H, m), 8.68 (1H, m), 8.38 (1H, dd, J 1.3, 4.6 Hz), 8.24 (1H, d, J 7.5

Hz), 8.09 (1H, dd, J 1.3, 8.2 Hz), 7.74 (1H, dd, J 1.8, 10.5 Hz), 7.59-7.57 (1H, m), 7.44 (1H, dd, J 4.7, 8.2 Hz), 7.39-7.34 (1H, m), 4.05-3.97 (1H, m), 3.32-3.27 (2H, m), 3.03-2.87 (2H, m), 2.00-1.97 (2H, m), 1.82-1.71 (2H, m). LCMS RT 2.40 minutes, (ES⁻) 495 (M-H)⁻, (ES⁺) 497 (M+H)⁺.

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EXAMPLE 44

(3-Aminoazetidin-1-yl)-{2-[(2-fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridin-3-yl}-methanone

- 10 Prepared from Example 39 (90 mg, 0.16 mmol) by the method of Example 30. The reaction mixture was concentrated *in vacuo* to give a yellow gum, which was dissolved in methanol (5 mL) and water (5 mL) and basified to pH 10 with 25% aq. ammonium hydroxide. The aqueous solution was concentrated *in vacuo* onto SiO₂, and the crude product was subjected to column chromatography (SiO₂, 95:4:1 DCM/
- 15 methanol/25% aq. ammonium hydroxide). The *title compound* was freeze-dried overnight from acetonitrile/methanol/water to give a cream-coloured powder (31 mg, 42%). δ_{H} (DMSO-*d*₆) 8.33 (1H, dd, J 1.5, 4.7 Hz), 7.94 (1H, dd, J 1.5, 8.1 Hz), 7.73 (1H, dd, J 1.9, 10.5 Hz), 7.54 (1H, ddd, J 0.9, 0.9, 8.4 Hz), 7.38 (1H, dd, J 4.7, 8.1 Hz), 7.31-7.26 (1H, m), 4.23-4.11 (2H, m), 3.72-3.59 (3H, m). LCMS RT 3.00 minutes, (ES⁻) 467
- 20 (M-H)⁻, (ES⁺) 469 (M+H)⁺.

EXAMPLE 45

- 25 2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylic acid bis(2-hydroxy-ethyl)amide

- Prepared from Intermediate 7 (150 mg, 0.36 mmol), 1-hydroxybenzotriazole (98 mg, 0.72 mmol), *N*-methylmorpholine (0.11 mL, 0.99 mmol), 1-(3-dimethylamino-propyl)-3-carbodiimide hydrochloride (139 mg, 0.72 mmol) and diethanolamine (76 mg, 0.72 mmol), by the method of Example 22. The crude product was subjected to column
- 30 chromatography (SiO₂, EtOAc, twice) to give the *title compound*, which was freeze-dried overnight from acetonitrile/water to give a cream-coloured powder (62 mg, 34%). δ_{H} (DMSO-*d*₆) 8.79 (1H, br s), 8.38 (1H, dd, J 1.5, 4.7 Hz), 7.77 (1H, dd, J 1.5, 8.1 Hz), 7.67

(1H, dd, J 1.9, 10.5 Hz), 7.69-7.46 (1H, m), 7.38 (1H, dd, J 4.7, 8.1 Hz), 7.18-7.12 (1H, m), 4.83 (2H, br s), 3.30 (8H, s). LCMS RT 3.01 minutes, (ES⁺) 502 (M+H)⁺.

EXAMPLE 46

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{2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridin-3-yl}-(3-hydroxyazetidin-1-yl)-methanone

Prepared from Intermediate 7 (225 mg, 0.54 mmol), 1-hydroxybenzotriazole (147 mg, 1.08 mmol), *N*-methylmorpholine (0.16 mL, 1.48 mmol), 1-(3-dimethylamino-propyl)-3-carbodiimide hydrochloride (208 mg, 1.08 mmol) and 3-hydroxyazetidine hydrochloride (120 mg, 1.08 mmol), by the method of Example 22. After chromatography, the *title compound* was recrystallised from methanol/ether to give a white powder (125 mg, 49%). δ_{H} (DMSO-*d*₆) 9.60 (1H, s), 8.35-8.34 (1H, m), 7.94 (1H, dd, J 1.4, 8.1 Hz), 7.75-7.71 (1H, m), 7.57-7.54 (1H, m), 7.41-7.37 (1H, m), 7.31-7.25 (1H, m), 5.68 (1H, d, J 6.0 Hz), 4.47-4.44 (1H, m), 4.21-4.16 (2H, m), 3.79-3.74 (2H, m). LCMS RT 3.31 minutes, (ES⁺) 470 (M+H)⁺.

EXAMPLE 47

20 {2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridin-3-yl}-(3*R*)-3-hydroxypyrrolidin-1-yl]-methanone

Prepared from Intermediate 7 (150 mg, 0.36 mmol), 1-hydroxybenzotriazole (98 mg, 0.72 mmol), *N*-methylmorpholine (0.11 mL, 0.99 mmol), 1-(3-dimethylamino-propyl)-3-carbodiimide hydrochloride (139 mg, 0.72 mmol) and (*R*)-3-hydroxypyrrolidine (63 mg, 0.72 mmol), by the method of Example 22. After chromatography, the *title compound* was freeze-dried overnight from acetonitrile/water to give a cream-coloured powder (116 mg, 66%). δ_{H} (DMSO-*d*₆) 9.20 (1H, s), 8.35 (1H, dd, J 1.5, 4.7 Hz), 7.81 (1H, dd, J 1.5, 8.1 Hz), 7.67 (1H, dd, J 1.9, 10.5 Hz), 7.50-7.47 (1H, m), 7.36 (1H, dd, J 4.7, 8.1 Hz), 7.17-7.11 (1H, m), 4.91 (1H, s), 4.22 (1H, s), 3.54-3.30 (3H, m), 3.21-3.17 (1H, m), 1.90-1.74 (2H, m). LCMS RT 3.18 minutes, (ES⁺) 484 (M+H)⁺.

EXAMPLE 48

{2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridin-3-yl}-[(3*S*)-3-hydroxypyrrolidin-1-yl]-methanone

Prepared from Intermediate 7 (150 mg, 0.36 mmol), 1-hydroxybenzotriazole (98 mg, 0.72 mmol), *N*-methylmorpholine (0.11 mL, 0.99 mmol), 1-(3-dimethylamino-propyl)-3-carbodiimide hydrochloride (139 mg, 0.72 mmol) and (*S*)-3-hydroxypyrrolidine (63 mg, 0.72 mmol), by the method of Example 47. The *title compound* was obtained as a cream-coloured powder (105 mg, 60%). δ_{H} (DMSO- d_6) 9.20 (1H, s), 8.35 (1H, dd, *J* 1.5, 4.7 Hz), 7.81 (1H, dd, *J* 1.5, 8.1 Hz), 7.67 (1H, dd, *J* 1.9, 10.5 Hz), 7.50-7.47 (1H, m), 7.36 (1H, dd, *J* 4.7, 8.1 Hz), 7.17-7.11 (1H, m), 4.91 (1H, s), 4.22 (1H, s), 3.54-3.30 (3H, m), 3.21-3.17 (1H, m), 1.90-1.74 (2H, m). LCMS RT 3.17 minutes, (ES^+) 484 ($\text{M}+\text{H}$) $^+$.

EXAMPLE 49

{2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridin-3-yl}-[2-(hydroxymethyl)-piperidin-1-yl]-methanone

Prepared from Intermediate 7 (150 mg, 0.36 mmol), 1-hydroxybenzotriazole (98 mg, 0.72 mmol), *N*-methylmorpholine (0.11 mL, 0.99 mmol), 1-(3-dimethylamino-propyl)-3-carbodiimide hydrochloride (139 mg, 0.72 mmol) and 2-piperidinemethanol (83 mg, 0.72 mmol), by the method of Example 22. After chromatography, the *title compound* was recrystallised from EtOAc/hexanes to give a pale yellow powder (44 mg, 24%). δ_{H} (DMSO- d_6 , 130°C) 8.38 (1H, dd, *J* 1.5, 4.7 Hz), 7.83 (1H, dd, *J* 1.5, 8.0 Hz), 7.59 (1H, dd, *J* 1.9, 10.5 Hz), 7.47 (1H, d, *J* 8.5 Hz), 7.35 (1H, dd, *J* 4.7, 8.0 Hz), 7.16 (1H, dd, *J* 8.8, 8.8 Hz), 4.30 (1H, br s), 4.21 (1H, m), 3.89 (1H, m), 3.65-3.60 (1H, m), 3.51-3.47 (1H, m), 3.03-2.97 (1H, m), 1.74-1.72 (1H, m), 1.65-1.56 (4H, m), 1.37 (1H, m). LCMS RT 2.86 minutes, (ES^-) 510 ($\text{M}-\text{H}$) $^-$, (ES^+) 512 ($\text{M}+\text{H}$) $^+$.

EXAMPLE 50

{2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridin-3-yl}-[(3*S*)-3-(hydroxymethyl)-morpholin-4-yl]-methanone

Prepared from Intermediate 7 (150 mg, 0.36 mmol), 1-hydroxybenzotriazole (98 mg, 0.72 mmol), *N*-methylmorpholine (0.11 mL, 0.99 mmol), 1-(3-dimethylamino-

propyl)-3-carbodiimide hydrochloride (139 mg, 0.72 mmol) and (3*S*)-3-(hydroxymethyl)-morpholine (85 mg, 0.72 mmol), by the method of Example 22. After chromatography, the *title compound* was freeze-dried overnight from acetonitrile/water to give a cream-coloured powder (81 mg, 44%). δ_{H} (DMSO- d_6 , 120°C) 8.37-8.36 (1H, m), 7.85-7.83 (1H, m), 7.60 (1H, dd, J 1.8, 10.5 Hz), 7.49-7.47 (1H, m), 7.35 (1H, dd, J 4.7, 8.0 Hz), 7.15 (1H, dd, J 8.7, 8.7 Hz), 3.99 (1H, m), 3.85 (1H, d, J 11.6 Hz), 3.80-3.77 (1H, m), 3.70-3.67 (1H, m), 3.65-3.56 (2H, m), 3.48-3.45 (1H, m), 3.34 (1H, m), 3.27-3.21 (1H, m). LCMS RT 2.60 minutes, (ES⁻) 512 (M-H)⁻, (ES⁺) 514 (M+H)⁺.

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EXAMPLE 51

4-{2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carbonyl}-(3*R*)-3-(hydroxymethyl)piperazine-1-carboxylic acid *tert*-butyl ester

Prepared from Intermediate 7 (150 mg, 0.36 mmol), 1-hydroxybenzotriazole (98 mg, 0.72 mmol), *N*-methylmorpholine (0.11 mL, 0.99 mmol), 1-(3-dimethylamino-propyl)-3-carbodiimide hydrochloride (139 mg, 0.72 mmol) and (2*R*)-4-BOC-2-(hydroxymethyl)piperazine (157 mg, 0.72 mmol), by the method of Example 22. The crude product was subjected to column chromatography (SiO₂, 1:1 hexanes/EtOAc) to give the *title compound*, which was evaporated from ether to give a pale pink, hard foam (95 mg, 43%). δ_{H} (DMSO- d_6 , 120°C) 8.53 (1H, br s), 8.38-8.37 (1H, m), 7.86-7.84 (1H, m), 7.60 (1H, dd, J 1.7, 10.5 Hz), 7.49 (1H, d, J 8.5 Hz), 7.36 (1H, dd, J 4.7, 8.0 Hz), 7.19-7.15 (1H, dd, J 8.5, 8.7 Hz), 4.52 (1H, br s), 4.16 (1H, m), 3.95 (1H, d, J 13.5 Hz), 3.88-3.81 (2H, m), 3.49-3.43 (2H, m), 3.14-3.10 (1H, m), 3.02-2.95 (1H, m), 1.43 (9H, s). LCMS RT 2.98 minutes, (ES⁺) 613 (M+H)⁺.

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EXAMPLE 52

2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-7-oxide

Example 8 (250 mg, 0.55 mmol) was suspended in a mixture of ethanol (20 mL) and water (10 mL). Lithium hydroxide hydrate (24.0 mg, 0.57 mmol) was added and the mixture heated to reflux for 24 hours. After concentration and freeze-drying, the mixture was purified by chromatography (silica, dichloromethane then 2% MeOH in dichloromethane). The *title compound* was obtained as an off-white solid (50 mg, 24%).

30

δ_H (DMSO- d_6) 9.42 (1H, br s), 8.13 (1H, dd, J 0.7, 6.2 Hz), 7.69 (1H, dd, J 1.9, 10.7 Hz), 7.54-7.51 (2H, m), 7.39-7.32 (2H, m), 6.73 (1H, s). LCMS (ES⁺) RT 2.84 minutes, 387 (M+H)⁺.

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EXAMPLE 53**2-[(2-Fluoro-4-iodophenyl)amino]-N-[2-(morpholin-4-yl)ethyl]thieno[2,3-*b*]pyridine-3-carboxamide**

Prepared from Example 1 (250 mg, 0.56 mmol) and 4-(2-aminoethyl)morpholine (292 mg, 2.24 mmol) by the method of Example 5. After chromatography (5% methanol, 95% dichloromethane) the *title compound* was obtained as an off-white solid (140 mg, 47%). δ_H (CDCl₃) 11.43 (1H, br s), 8.36 (1H, dd, J 1.4, 4.7 Hz), 8.03 (1H, dd, J 1.4, 8.2 Hz), 7.55-7.51 (2H, m), 7.44 (1H, dd, J 8.2, 8.2 Hz), 7.32 (1H, dd, J 4.7, 8.2 Hz), 6.84 (1H, br s), 3.80-3.77 (4H, m), 3.67-3.62 (2H, m), 2.73-2.69 (2H, m), 2.62-2.59 (4H, m). LCMS (ES⁺) RT 2.37 minutes, 527 (M+H)⁺.

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EXAMPLE 54**2-[4-({2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridin-3-yl}carbonyl)piperazin-1-yl]ethanol**

Prepared from Example 1 (250 mg, 0.56 mmol) and *N*-(2-hydroxyethyl)piperazine (292 mg, 2.24 mmol) by the method of Example 5. After chromatography (5% methanol, 95% dichloromethane) the *title compound* was obtained as a white solid (86 mg, 29%). δ_H (DMSO- d_6) 9.13 (1H, br s), 8.36 (1H, dd, J 1.5, 4.7 Hz), 7.80 (1H, dd, J 1.5, 8.1 Hz), 7.68 (1H, dd, J 1.9, 10.5 Hz), 7.49-7.45 (1H, m), 7.37 (1H, dd, J 4.7, 8.1 Hz), 7.10 (1H, dd, J 8.7, 8.7 Hz), 4.37 (1H, t, J 5.4 Hz), 3.50-3.40 (6H, m), 2.37-2.33 (6H, m). LCMS (ES⁺) RT 2.16 minutes, 527 (M+H)⁺.

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EXAMPLE 55

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3-(1,4-Diazepan-1-ylcarbonyl)-N-(2-fluoro-4-iodophenyl)thieno[2,3-*b*]pyridin-2-amine

Prepared from Example 1 (250 mg, 0.56 mmol) and homopiperazine (224 mg, 2.24 mmol) by the method of Example 5. After chromatography (10-15% methanol in

dichloromethane) the *title compound* was obtained as a pale yellow solid (180 mg, 64%). δ_H (CDCl₃) 8.99 (1H, br s), 8.34 (1H, dd, *J* 1.6, 4.7 Hz), 7.74 (1H, dd, *J* 1.6, 8.1 Hz), 7.47-7.43 (2H, m), 7.35 (1H, dd, *J* 8.5, 8.5 Hz), 7.28-7.22 (1H, m), 4.30-4.10 (1H, br m), 3.95-3.80 (1H, br m), 3.39-2.86 (6H, br m), 2.17-1.77 (3H, br m). LCMS (ES⁺) RT 2.17 minutes, 497 (M+H)⁺.

EXAMPLE 56

N-[3-(Dimethylamino)-2,2-dimethylpropyl]-2-[(2-fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxamide

Prepared from Example 1 (250 mg, 0.56 mmol) and *N,N*,2,2-tetramethyl-1,3-propanediamine (292 mg, 2.24 mmol) by the method of Example 5. After chromatography (5% methanol, 95% dichloromethane) the *title compound* was obtained as a pale yellow solid (60 mg, 20%). δ_H (DMSO-*d*₆) 10.81 (1H, br s), 9.10 (1H, br s), 8.24-8.21 (2H, m), 7.69-7.65 (1H, m), 7.55-7.52 (1H, m), 7.37-7.31 (2H, m), 3.29-3.27 (2H, m), 2.50-2.37 (8H, br m), 0.96 (6H, s). LCMS (ES⁺) RT 2.39 minutes, 527 (M+H)⁺.

EXAMPLE 57

2-[(2-Fluoro-4-iodophenyl)amino]-*N*-[3-(morpholin-4-yl)propyl]thieno[2,3-*b*]pyridine-3-carboxamide

Prepared from Example 1 (250 mg, 0.56 mmol) and 4-(3-aminopropyl)morpholine (323 mg, 2.24 mmol) by the method of Example 5. After chromatography (5% methanol, 95% dichloromethane) the *title compound* was obtained as a pale yellow solid (115 mg, 38%). δ_H (CDCl₃) 11.29 (1H, br s), 8.36 (1H, dd, *J* 1.4, 4.7 Hz), 7.99 (1H, dd, *J* 1.4, 8.2 Hz), 7.63-7.51 (2H, m), 7.47-7.41 (1H, m), 7.33-7.29 (1H, m), 7.12 (1H, br s), 3.70-3.64 (2H, m), 3.60-3.56 (4H, m), 2.58-2.54 (2H, m), 2.49-2.46 (4H, m), 1.90-1.82 (2H, m). LCMS (ES⁺) RT 2.34 minutes, 541 (M+H)⁺.

EXAMPLE 58

N-(2-Fluoro-4-iodophenyl)-3-(piperazin-1-ylcarbonyl)thieno[2,3-*b*]pyridin-2-amine

- Piperazine (3.90 g, 45.2 mmol) was dissolved in dry toluene (100 mL) under nitrogen. The mixture was placed in a water bath at 20°C and trimethylaluminium (2.0M in toluene, 22.6 mL, 45.2 mmol) added slowly. After 10 minutes, Example 1 (4.00 g, 0.56 mmol) was added. The mixture was heated to 100°C under nitrogen for 6 hours.
- 5 After cooling to room temperature, the mixture was poured onto a slurry of silica (100 g) in chloroform (400 mL) and methanol (200 mL). After agitation for 10 minutes, the mixture was allowed to stand overnight. Filtration, and concentration of the organic solvent *in vacuo*, gave crude material, which was purified by triturating with diethyl ether (50 mL), filtering and washing with diethyl ether (20 mL). The *title compound* was
- 10 isolated as a yellow solid (3.56 g, 82%), which could be used for further chemistry. The dihydrochloride salt of the *title compound* was prepared by dissolving the free base (1.60 g, 3.32 mmol) in dichloromethane (30 mL) and methanol (5 mL). HCl in ether (2.0M, 3.34 mL, 6.70 mmol) was added and the mixture concentrated *in vacuo*. Trituration with diethyl ether (40 mL) and filtration gave the dihydrochloride salt of the *title compound*
- 15 (1.80 g, 98%). δ_{H} (DMSO- d_6) 9.75 (0.25H, br s), 9.43 (1.75H, br s), 9.30 (1H, s), 8.36 (1H, dd, J 1.6, 4.7 Hz), 7.87 (1H, dd, J 1.6, 8.1 Hz), 7.72 (1H, dd, J 1.9, 10.6 Hz), 7.53 (1H, m), 7.39 (1H, dd, J 4.7, 8.1 Hz), 7.22 (1H, dd, J 8.5, 8.5 Hz), 3.75-3.58 (4H, m), 3.17-3.06 (4H, m). LCMS (ES $^+$) RT 2.19 minutes, 483 (M+H) $^+$.

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EXAMPLE 59

Ethyl [4-(2-[(2-fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridin-3-yl)carbonyl)-piperazin-1-yl]acetate

- Example 58 (300 mg, 0.62 mmol) was dissolved in dichloromethane (10 mL) and triethylamine (94 μ L, 0.65 mmol) and ethyl chloroacetate (56 μ L, 0.65 mmol) added. The mixture was heated to reflux for 12 hours. After cooling and partitioning between dichloromethane and water (25 mL each), the organic layer was dried (Na₂SO₄) and concentrated *in vacuo*. Purification by chromatography (silica, 3% methanol, 97% dichloromethane) gave the product as an oil, which was dissolved in diethyl ether (5 mL)
- 30 and concentrated under high vacuum to give the *title compound* as a white solid (240 mg, 68%). δ_{H} (CDCl₃) 9.11 (1H, br s), 8.37 (1H, dd, J 1.5, 4.7 Hz), 7.71 (1H, dd, J 1.5, 8.1 Hz), 7.53-7.49 (2H, m), 7.40 (1H, dd, J 8.4, 8.4 Hz), 7.32-7.28 (1H, m), 4.21 (2H, q, J 7.1

Hz), 3.75-3.61 (4H, m), 3.31 (2H, s), 2.79-2.62 (4H, m), 1.29 (3H, t, J 7.1 Hz). LCMS (ES⁺) RT 3.26 minutes, 569 (M+H)⁺.

EXAMPLE 60

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[4-({2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridin-3-yl}carbonyl)piperazin-1-yl]acetic acid

Example 59 (213 mg, 0.375 mmol) was dissolved in ethanol (7 mL) and water (7 mL). Sodium hydroxide (15.0 mg, 0.375 mmol) was added and the mixture stirred at room temperature for 18 hours. Freeze-drying gave the *title compound* as its sodium salt (200 mg, 99%). δ_H (DMSO- d_6) 9.29 (1H, br s), 8.22-8.17 (1H, br m), 7.68 (1H, br d, J 8.0 Hz), 7.56 (1H, br d, J 10.4 Hz), 7.40 (1H, br d, J 8.6 Hz), 7.28-7.20 (1H, br m), 7.07 (1H, dd, J 8.6, 8.6 Hz), 3.42-3.38 (4H, m), 2.65 (2H, s), 2.37-2.35 (4H, m). LCMS (ES⁺) RT 2.64 minutes, 541 (M+H)⁺.

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EXAMPLE 61

tert-Butyl (3*R*)-3-[(2-[(2-fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridin-3-yl)-carbonyl)amino]pyrrolidine-1-carboxylate

Prepared from Example 1 (250 mg, 0.56 mmol) and (*R*)-3-amino-1-*tert*-butoxycarbonylpyrrolidine (417 mg, 2.24 mmol) by the method of Example 5. After chromatography (25% ethyl acetate, 75% dichloromethane) the *title compound* was obtained as an off-white solid (45 mg, 13%). δ_H (DMSO- d_6) 10.27 (1H, br s), 8.35 (1H, dd, J 1.4, 4.7 Hz), 8.23 (1H, br d, J 6.5 Hz), 8.06 (1H, dd, J 1.4, 8.2 Hz), 7.74 (1H, dd, J 1.9, 10.5 Hz), 7.57 (1H, d, J 8.5 Hz), 7.43 (1H, dd, J 4.7, 8.2 Hz), 7.36 (1H, dd, J 8.6, 8.6 Hz), 4.46-4.40 (1H, br m), 3.57-3.54 (1H, m), 3.52-3.30 (3H, m), 2.15-2.05 (1H, br m), 1.95-1.85 (1H, br m), 1.41 (9H, s). LCMS (ES⁺) RT 3.70 minutes, 583 (M+H)⁺.

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EXAMPLE 62

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tert-Butyl (3*S*)-3-[(2-[(2-fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridin-3-yl)-carbonyl)amino]pyrrolidine-1-carboxylate

Prepared from Example 1 (250 mg, 0.56 mmol) and (*S*)-3-amino-1-*tert*-butoxycarbonylpyrrolidine (417 mg, 2.24 mmol) by the method of Example 5. After chromatography (25% ethyl acetate, 75% dichloromethane) the *title compound* was obtained as an off-white solid (190 mg, 58%). δ_{H} (DMSO- d_6) 10.27 (1H, br s), 8.35 (1H, dd, *J* 1.4, 4.7 Hz), 8.23 (1H, br d, *J* 6.5 Hz), 8.06 (1H, dd, *J* 1.4, 8.2 Hz), 7.74 (1H, dd, *J* 1.9, 10.5 Hz), 7.57 (1H, d, *J* 8.5 Hz), 7.43 (1H, dd, *J* 4.7, 8.2 Hz), 7.36 (1H, dd, *J* 8.6, 8.6 Hz), 4.46-4.40 (1H, br m), 3.57-3.54 (1H, m), 3.52-3.30 (3H, m), 2.15-2.05 (1H, br m), 1.95-1.85 (1H, br m), 1.41 (9H, s). LCMS (ES^+) RT 3.70 minutes, 583 ($\text{M}+\text{H}$) $^+$.

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EXAMPLE 63**2-[(2-Fluoro-4-iodophenyl)amino]-*N*-[(3*R*)-pyrrolidin-3-yl]thieno[2,3-*b*]pyridine-3-carboxamide**

Example 61 (40 mg, 0.069 mmol) was dissolved in dichloromethane (3 mL) and HCl in dioxane (4.0M, 1.0 mL, 4.0 mmol) was added. The mixture was stirred at room temperature for 18 hours. The resultant solid was filtered off and dried under vacuum at 40°C to give the dihydrochloride salt of the *title compound* (28 mg, 73%). δ_{H} (DMSO- d_6) 10.44 (1H, br s), 9.25 (2H, br m), 8.37-8.31 (2H, m), 8.21 (1H, dd, *J* 1.3, 8.2 Hz), 7.76 (1H, dd, *J* 1.8, 10.4 Hz), 7.61 (1H, d, *J* 8.5 Hz), 7.45-7.39 (2H, m), 4.61-4.57 (1H, m), 3.45-3.23 (4H, m), 2.27-2.15 (1H, m), 2.09-1.98 (1H, m). LCMS (ES^+) RT 2.30 minutes, 483 ($\text{M}+\text{H}$) $^+$.

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EXAMPLE 64**2-[(2-Fluoro-4-iodophenyl)amino]-*N*-[(3*S*)-pyrrolidin-3-yl]thieno[2,3-*b*]pyridine-3-carboxamide**

Example 62 (170 mg, 0.069 mmol) was dissolved in dichloromethane (4 mL) and HCl in dioxane (4.0M, 4.0 mL, 16.0 mmol) was added. The mixture was stirred at room temperature for 18 hours. The resultant solid was filtered off and dried under vacuum at 40°C to give the dihydrochloride salt of the *title compound* (150 mg, 92%). δ_{H} (DMSO- d_6) 10.44 (1H, br s), 9.25 (2H, br m), 8.37-8.31 (2H, m), 8.21 (1H, dd, *J* 1.3, 8.2 Hz), 7.76 (1H, dd, *J* 1.8, 10.4 Hz), 7.61 (1H, d, *J* 8.5 Hz), 7.45-7.39 (2H, m), 4.61-4.57 (1H, m),

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3.45-3.23 (4H, m), 2.27-2.15 (1H, m), 2.09-1.98 (1H, m). LCMS (ES⁺) RT 2.30 minutes, 483 (M+H)⁺.

EXAMPLE 65

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2-[(2-Fluoro-4-iodophenyl)amino]-N-(1-methylpiperidin-4-yl)thieno[2,3-*b*]pyridine-3-carboxamide

Prepared from Example 1 (250 mg, 0.56 mmol) and 4-amino-1-methylpiperidine (255 mg, 2.24 mmol) by the method of Example 5. After chromatography (10% methanol, 90% dichloromethane) the crude material was dissolved in dichloromethane (2 mL) and 2.0M HCl in diethyl ether (2 mL) was added. The resultant solid was filtered off to give the dihydrochloride salt of the *title compound* as a yellow solid (145 mg, 44%).

δ_H (DMSO-*d*₆) 10.62 (1H, br s), 10.37 (0.8H, s), 10.26 (0.2H, s), 8.40-8.36 (1H, m), 8.31-8.28 (0.8H, m), 8.22-8.20 (0.2H, m), 8.19-8.16 (0.2H, m), 8.10-8.07 (0.8H, m), 7.75-7.71 (1H, m), 7.59-7.56 (1H, m), 7.47-7.31 (2H, m), 4.05 (1H, br m), 3.45-3.05 (5H, m), 2.70 (3H, d, *J* 6.0 Hz), 2.03-1.85 (4H, m). LCMS (ES⁺) RT 2.34 minutes, 511 (M+H)⁺.

EXAMPLE 66

20 {2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridin-3-yl}-[(2*R*)-2-(methoxymethyl)-pyrrolidin-1-yl]-methanone

From Intermediate 14 (285 mg, 0.66 mmol), 2M trimethylaluminium in hexane (1.6 mL, 3.30 mmol) and (*R*)-2-(methoxymethyl)pyrrolidine (383 mg, 3.30 mmol) by the method of Example 5, to give the *title compound* (17 mg). δ_H (DMSO-*d*₆) 9.17 (1H, br s), 8.37 (1H, dd, *J* 4.6, 1.3 Hz), 7.78 (1H, d, *J* 7.7 Hz), 7.76 (1H, dd, *J* 10.6, 1.8 Hz), 7.46 (1H, d, *J* 8.5 Hz), 7.37 (1H, d, *J* 8.0, 4.6 Hz), 7.05 (1H, t, *J* 8.5 Hz), 4.10-4.00 (1H, br m), 3.33-3.01 (7H, br m), 1.90-1.64 (4H, br m). LCMS (ES⁺) RT 3.27 minutes, 215 (M+H)⁺.

EXAMPLE 67

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2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylic acid (cyclopropylmethyl)amide

From Intermediate 14 (450 mg, 1.05 mmol), 2M trimethylaluminium in hexane (2.6 mL, 5.26 mmol) and (aminomethyl)cyclopropane (374 mg, 5.26 mmol) by the method of Example 5, to give the *title compound* (250 mg). δ_H (DMSO- d_6) 10.68 (1H, br s), 8.36 (1H, d, J 3.8 Hz), 8.17 (1H, d, J 8.1 Hz), 8.15-8.00 (1H, br m), 7.75 (1H, d, J 10.4 Hz), 7.60 (1H, d, J 7.6 Hz), 7.47-7.38 (2H, br m), 3.18 (2H, t, J 6.2 Hz), 1.10-1.03 (1H, br m), 0.47-0.41 (2H, br m), 0.28-0.23 (2H, br m). LCMS (ES⁺) RT 3.54 minutes, 468 (M+H)⁺.

EXAMPLE 68

10

2-[(2-Fluoro-4-iodophenyl)amino]-7-oxythieno[2,3-*b*]pyridine-3-carboxylic acid (*N*-methoxy-*N*-methyl)amide

To a solution of Intermediate 16 (260 mg, 1.12 mmol) in DMSO was added sodium hydride (50 mg, 1.23 mmol), and the reaction stirred for 10 minutes. Intermediate 1 (328 mg, 1.18 mmol) was added and the reaction stirred for a further 1 h at ambient temperature. The reaction was poured onto water and extracted into ethyl acetate. The organic phase was washed with brine, dried (magnesium sulphate) and concentrated *in vacuo*. The crude product was purified by chromatography (SiO₂; 10% methanol in ethyl acetate) yielding the required product as a pale yellow solid (64 mg). δ_H (DMSO- d_6) 9.41 (1H, s), 8.20 (1H, dd, J 5.9, 1.0 Hz), 7.74 (1H, dd, J 10.3, 1.9 Hz), 7.57-7.54 (1H, m), 7.48-7.38 (2H, m), 7.22 (1H, t, J 8.6 Hz), 3.47 (3H, s), 3.17 (3H, s). LCMS (ES⁺) RT 2.70 minutes, 474 (M+H)⁺.

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EXAMPLE 69

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2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridine-3-carboxylic acid (*N*-methoxy-*N*-methyl)amide

Example 68 (64 mg, 0.13 mmol) and triphenyl phosphine (177 mg, 0.68 mmol) in THF (1 mL) were heated at 65°C overnight. Phosphorus trichloride (34 mg, 0.39 mmol) was added and the reaction stirred at ambient temperature for 90 minutes. The reaction was quenched with sodium hydrogen carbonate solution and the product extracted into DCM, dried (magnesium sulphate) and concentrated *in vacuo*. After preparative HPLC, the required product (10 mg) was obtained as an off-white solid. δ_H (DMSO- d_6) 9.23

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(1H, s), 8.35 (1H, dd, J 4.7, 1.6 Hz), 7.84 (1H, dd, J 8.1, 1.6 Hz), 7.70 (1H, dd, J 10.3, 1.9 Hz), 7.53 (1H, d, J 8.4 Hz), 7.37 (1H, dd, J 8.1, 4.7 Hz), 7.22 (1H, t, J 8.6 Hz), 3.47 (3H, s), 3.20 (3H, s). LCMS (ES^+) RT 3.23 minutes, 458 ($M+H$) $^+$.

5

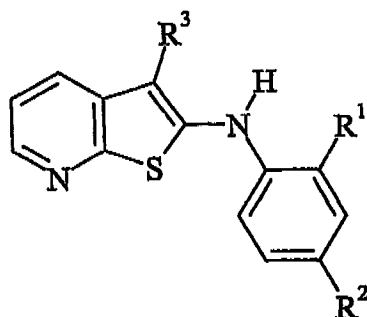
EXAMPLE 70

{2-[(2-Fluoro-4-iodophenyl)amino]thieno[2,3-*b*]pyridin-3-yl}-[(2*R*)-2-(hydroxymethyl)-piperazin-1-yl]-methanone

A solution of Example 51 (80 mg, 0.13 mmol) in methanol (2 mL) was treated
10 with 4M HCl in 1,4-dioxane (5 mL) and stirred at r.t. for 3 h. The reaction mixture was concentrated *in vacuo* to give a yellow gum, which was dissolved in methanol (20 mL) and water (5 mL), then basified to pH 11 with 25% aq. ammonium hydroxide. The aqueous solution was extracted with DCM (3 x 25 mL), and the organic extracts were combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was
15 subjected to column chromatography (SiO_2 , 95:4:1 DCM/methanol/25% aq. ammonium hydroxide) to give the *title compound* as a mixture of 2 rotamers, which were freeze-dried overnight from acetonitrile/water to give a cream-coloured powder (63 mg, 94%). δ_H (DMSO- d_6 , 120°C, contains rotamers) 8.37-8.36 (1H, m), 8.29-8.28 (0.44H, m), 8.33 (0.56H, dd, J 1.4, 8.0 Hz), 7.75 (0.44H, dd, J 1.8, 10.0 Hz), 7.68-7.66 (0.44H, m), 7.58 (0.56H, dd, J 1.9, 10.5 Hz), 7.48-7.44 (1H, m), 7.39-7.33 (1H, m), 7.17-7.13 (0.56H, m),
20 4.31-4.29 (1H, m), 4.00 (1H, m), 3.74-3.60 (2H, m), 3.10-2.83 (3H, m), 2.76-2.65 (2H, m), 2.60-2.53 (1H, m). LCMS RT 2.07 and 1.95 minutes, (ES^+) 513 ($M+H$) $^+$.

Claims:

1. A compound of formula (I), or a pharmaceutically acceptable salt, solvate or *N*-oxide thereof:



(I)

wherein

R¹ represents hydrogen, halogen or C₁₋₆ alkyl;

R² represents halogen or C₁₋₆ alkyl;

R³ represents hydrogen, cyano, -CO₂R^a, -CONR^bR^c or -CON(OR^b)R^c;

R^a represents C₁₋₆ alkyl;

R^b represents hydrogen; or C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents; and

R^c represents hydrogen or C₁₋₆ alkyl (optionally substituted by hydroxy); or

R^b and R^c, when taken together with the nitrogen atom to which they are both attached, represent azetidiny, pyrrolidiny, piperidiny, morpholiny, thiomorpholiny, piperaziny, homopiperidiny, homomorpholiny or homopiperaziny, any of which groups may be optionally substituted by one or more substituents.

2. A compound as claimed in claim 1 wherein R^b represents hydrogen; or C₁₋₆ alkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl or C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, any of which groups may be optionally substituted by one or more substituents.

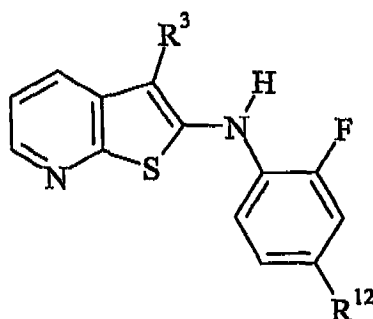
3. A compound as claimed in claim 1 wherein the cyclic moiety $-NR^bR^c$ represents azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl or homopiperazin-1-yl, any of which groups may be optionally substituted by one or more substituents.

5

4. A compound as claimed in any one of the previous claims wherein the substituents on R^b , or on the cyclic moiety $-NR^bR^c$, are selected from C_{1-6} alkyl, C_{1-6} alkoxy(C_{1-6})alkyl, hydroxy, hydroxy(C_{1-6})alkyl, amino, amino(C_{1-6})alkyl, carboxymethyl, C_{2-6} alkoxycarbonyl, C_{2-6} alkoxycarbonyl(C_{1-6})alkyl, di(C_{1-6})alkylamino, C_{2-6} alkoxycarbonylamino and C_{2-6} alkoxycarbonylamino(C_{1-6})alkyl.

10

5. A compound as claimed in claim 1 represented by formula (II), and pharmaceutically acceptable salts, solvates and *N*-oxides thereof:



(II)

15

wherein

R^{12} represents halogen; and

R^3 is as defined in claim 1.

20

6. A compound as claimed in claim 5 wherein R^{12} represents bromo or iodo.

7. A compound as claimed in claim 1 as herein specifically disclosed in any one of the Examples.

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8. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt, solvate or *N*-oxide thereof, in association with a pharmaceutically acceptable carrier.

5 9. The use of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt, solvate or *N*-oxide thereof, for the manufacture of a medicament for the treatment and/or prevention of disorders for which the administration of a selective MEK inhibitor is indicated.

10 10. A method for the treatment and/or prevention of disorders for which the administration of a selective MEK inhibitor is indicated which comprises administering to a patient in need of such treatment an effective amount of a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt, solvate or *N*-oxide thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/000310

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D495/04 A61K31/4365

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

B. FIELDS SEARCHED

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

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

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

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/023818 A (AXXIMA PHARMACEUTICALS AG [DE]; KOUL ANIL [BE]; KLEBL BERT [DE]; MUELL) 17 March 2005 (2005-03-17) cited in the application claims 1,19	1-10
A	WO 2004/000846 A (CELLTECH R & D LTD [GB]; BROOKINGS DANIEL CHRISTOPHER [GB]; DAVIS JERE) 31 December 2003 (2003-12-31) page 29, lines 4-14 claim 1	1-10
A	WO 2004/113348 A (CELLTECH R & D LTD [GB]; BROOKINGS DANIEL CHRISTOPHER [GB]; DAVIS JERE) 29 December 2004 (2004-12-29) page 27, lines 10-20 claim 1	1-10
-/-		

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

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Date of mailing of the international search report

14/06/2007

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INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2007/000310

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2004/138251 A1 (BOSCHELLI DIANE HARRIS [US] ET AL) 15 July 2004 (2004-07-15) paragraph [0748] claim 1	1-10
A	BREMNER, D. H. ET AL: "The synthesis of thienopyridines from ortho-halogenated pyridine derivatives. Part 3" SYNTHESIS, (8), 1095-1097 CODEN: SYNTBF; ISSN: 0039-7881, 1998, XP002434659 page 1095; compound 12 page 1096; compound 18	1-4
A	ERIAN, AYMAN WAHBA ET AL: "An Easy Direct Conversion of Pyridine- and Pyrimidinethiones into Multi-Fused Heterocyclic Compounds" BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, 71(10), 2387-2391 CODEN: BCSJAB; ISSN: 0009-2673, 1998, XP002434660 page 2387; compound 7B	1-4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2007/000310

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. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box 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

Information on patent family members

International application No

PCT/GB2007/000310

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005023818 A	17-03-2005	AU 2004270394 A1 CA 2572750 A1	17-03-2005 17-03-2005
WO 2004000846 A	31-12-2003	AU 2003253087 A1 BR 0311842 A CA 2487718 A1 CN 1671715 A EP 1551848 A1 IS 7652 A JP 2005530838 T KR 20060013331 A MX PA04012746 A NZ 537740 A UA 78578 C2 US 2006004025 A1	06-01-2004 15-03-2005 31-12-2003 21-09-2005 13-07-2005 18-01-2005 13-10-2005 09-02-2006 23-03-2005 31-03-2006 10-04-2007 05-01-2006
WO 2004113348 A	29-12-2004	AU 2004249498 A1 CA 2528603 A1 EP 1638979 A1 US 2006247269 A1	29-12-2004 29-12-2004 29-03-2006 02-11-2006
US 2004138251 A1	15-07-2004	US 2004242883 A1	02-12-2004

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(19) Organización Mundial de Propiedad
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(43) Fecha de Publicación Internacional
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(10) Número de Publicación Internacional
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PCT

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(74) Agente: **THOMPSON, John**; UCB Celltech, 208 Bath Road, Slough, Berkshire SL1 3WE (GB).

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

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(71) Solicitante (para todos los Estados designados menos los Estados Unidos): **UCB PHARMA S.A.** [BE/BE]; 60 Allée De La Recherche, B-1070 Brussels (BE)

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(72) Inventores; y

(75) Inventores/Solicitantes (para los Estados Unidos de América únicamente): **HUTCHINGS, Martin, Clive**; UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **ARCHIBALD, Sarah, Catherine**; UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **BROOKINGS, Daniel, Christopher**; UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **DAVIS, Jeremy, Martin**; UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **JOHNSON, James, Andrew**; UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **ANGHAM, Barry, John**; UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **NEUSS, Judi, Charlotte**; UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB).

Publicado:

- con el informe de búsqueda internacional
- antes del vencimiento de la fecha límite para modificar las reivindicaciones y a ser publicada nuevamente en el evento de recibir las modificaciones.

Para códigos de dos letras y otras abreviaciones, referirse a las "Notas de guía sobre Códigos y Abreviaturas" que aparecen al comienzo de cada edición de la Gaceta del PCT

(54) Título: DERIVADOS DE TIENO-PIRIDINA COMO INHIBIDORES DE MEK

(57) Resumen: Una serie de derivados de tieno[2,3-b]piridina que están sustituidos en la posición 2 con un resto anilino sustituido, que son inhibidores selectivos de las enzi-mas MEK (MAPKK) humanas, son por consiguiente beneficiosos en medicina, por ejemplo en el tratamiento de afecciones inflamatorias, autoinmunes, cardiovasculares, proliferativas (con inclusión de las oncológicas) y nociceptivas.

DERIVADOS DE TIENO-PIRIDINA COMO INHIBIDORES DE MEK**Resumen:**

Una serie de derivados de tieno[2,3-*b*]piridina que es-
5 tán sustituidos en la posición 2 con un resto anilino
sustituido, que son inhibidores selectivos de las enzi-
mas MEK (MAPKK) humanas, son por consiguiente beneficio-
sos en medicina, por ejemplo en el tratamiento de afec-
ciones inflamatorias, autoinmunes, cardiovasculares,
10 proliferativas (con inclusión de las oncológicas) y no-
ciceptivas.

DERIVADOS DE TIENO-PIRIDINA COMO INHIBIDORES DE MEK

La presente invención se refiere a una clase de derivados de tieno-piridina y a su uso en terapia. Más particularmente, la invención se refiere a derivados de tieno[2,3-b]piridina que están sustituidos en la posición 2 con un resto anilino sustituido. Estos compuestos son inhibidores selectivos de las enzimas MEK (MAPKK), y son por consiguiente beneficiosos como agentes farmacéuticos, especialmente en el tratamiento de condiciones adversas inflamatorias, autoinmunes, cardiovasculares, proliferativas (con inclusión de las oncológicas) y nociceptivas).

Las enzimas MEK están implicadas en una diversidad de funciones fisiológicas y patológicas que se cree intervienen en una serie de enfermedades humanas. Estas funciones se resumen en los párrafos [0004] y [0005] del documento US 2005/0049276 A1.

Los compuestos de uso en la presente invención, al ser inhibidores potentes y selectivos de MEK, son por tanto beneficiosos en el tratamiento y/o la prevención de diversas dolencias humanas. Éstas incluyen trastornos autoinmunes e inflamatorios tales como artritis reumatoide, osteoartritis, esclerosis múltiple, asma, enfermedad inflamatoria del intestino, psoriasis y rechazo de trasplantes; trastornos cardiovasculares que incluyen trombosis, hipertrofia cardíaca, hipertensión, y contractilidad irregular del corazón (v.g. durante la insuficiencia cardíaca); trastornos proliferativos tales como restenosis, y afecciones oncológicas que incluyen leucemia, glioblastoma, linfoma, melanoma, y cánceres humanos de hígado, huesos, piel, cerebro, páncreas, pulmón, mama, estómago, colon, recto, próstata, ovario y cuello uterino; así como trastornos de dolor y noci-

ceptivos, que incluyen dolor crónico y dolor neuropático.

Adicionalmente, los compuestos de uso en la presente invención pueden ser beneficiosos como estándares farmacológicos para uso en el desarrollo de nuevos tests biológicos y en la investigación de nuevos agentes farmacológicos. Así, los compuestos de uso en esta invención pueden ser útiles como radioligandos en ensayos para detección de compuestos capaces de fijarse a las enzimas MEK humanas.

Inhibidores de MEK basados en un sistema bicíclico de anillos aromáticos unido a un resto anilino sustituido se conocen en la técnica. Ejemplos de publicaciones relevantes incluyen WO 2005/051906, WO 2005/023251, US-A-2005/0049276, WO 2005/009975, WO 03/077914 y WO 03/077855.

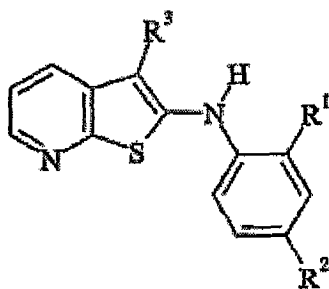
El documento WO 2005/023818 describe una gama extensa de compuestos basados en un sistema bicíclico de anillos aromáticos condensados, que abarca genéricamente derivados de tieno-piridina unidos a un resto anilino sustituido, pero no describe específicamente en absoluto ningún compuesto concreto de este tipo. No se adscribe actividad ninguna farmacológica discreta, en términos de un mecanismo farmacológico identificable, a los compuestos descritos en dicho documento, pero se afirma sin embargo que los mismos son útiles *inter alia* en el tratamiento de enfermedades celulares proliferativas tales como el cáncer. El documento US-A-2003/0220365 es también relevante en un contexto afín.

Sin embargo, en ningún lugar de la técnica anterior se encuentra la descripción precisa de una clase de derivados de tieno[2,3-*b*]piridina unidos en la posición 2 a un resto anilino sustituido. Se ha encontrado ahora que

tales compuestos son particularmente valiosos como inhibidores selectivos de las enzimas MEK.

Los compuestos de la presente invención son inhibidores potentes y selectivos de MEK que tienen una afinidad de fijación (CI_{50}) para la enzima MEK1 y/o MEK2 humana de 50 μM o menos, generalmente de 20 μM o menos, usualmente de 5 μM o menos, típicamente de 1 μM o menos, convenientemente de 500 nM o menos, idealmente de 100 nM o menos, y preferiblemente de 20 nM o menos (las personas expertas apreciarán que una cifra CI_{50} menor designa un compuesto *más activo*). Los compuestos de la invención pueden poseer al menos una afinidad selectiva de 10 veces, típicamente al menos una afinidad selectiva de 20 veces, convenientemente al menos una afinidad selectiva de 50 veces, e idealmente al menos una afinidad selectiva de 100 veces, para la enzima MEK-1 y/o MEK-2 humana con relación a otras quinasas humanas.

La presente invención proporciona un compuesto de fórmula (I), o una sal farmacéuticamente aceptable, solvato o *N*-óxido del mismo:



(I)

en donde

- 25 R^1 representa hidrógeno, halógeno o alquilo C_{1-6} ;
 R^2 representa halógeno o alquilo C_{1-6} ;
 R^3 representa hidrógeno, ciano, $-CO_2R^a$, $-CONR^bR^c$ o $-CON(OR^b)R^c$;
 R^a representa alquilo C_{1-6} ;

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R^b representa hidrógeno; o alquilo C₁₋₆, cicloalquilo C₃₋₇, cicloalquil C₃₋₇-alquilo(C₁₋₆), arilo, arilalquilo(C₁₋₆), heterocicloalquilo C₃₋₇, heterocicloalquil C₃₋₇-alquilo(C₁₋₆), heteroarilo o heteroarilalquilo(C₁₋₆), pudiendo estar cualquiera de dichos grupos sustituido opcionalmente con uno o más sustituyentes; y

R^c representa hidrógeno o alquilo C₁₋₆ (sustituido opcionalmente con hidroxilo); o

10 R^b y R^c, cuando se consideran junto con el átomo de nitrógeno al cual están unidos ambos, representan aze-
tidinilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, homopiperidinilo, homomorfolinilo u homopiperazinilo, pudiendo estar cual-
15 quiera de dichos grupos sustituido opcionalmente con uno o más sustituyentes.

La presente invención proporciona también un compuesto de fórmula (I) como se ha descrito arriba, o una sal, solvato o N-óxido farmacéuticamente aceptable del mismo, en donde

R¹ y R² son como se define arriba;

R³ representa ciano, -CO₂R^a, -CONR^bR^c o -CON(OR^b)R^c;

R^a representa alquilo C₁₋₆;

25 R^b representa hidrógeno; o alquilo C₁₋₆, cicloalquilo C₃₋₇, cicloalquil C₃₋₇-alquilo(C₁₋₆), arilo, arilalquilo(C₁₋₆), heterocicloalquilo C₃₋₇, heterocicloalquil C₃₋₇-alquilo(C₁₋₆), heteroarilo o heteroarilalquilo(C₁₋₆), pudiendo estar cualquiera de dichos grupos sustituido opcionalmente con uno o más sustituyentes; y

R^c representa hidrógeno o alquilo C₁₋₆; o

35 R^b y R^c, cuando se consideran junto con el átomo de nitrógeno al cual están unidos ambos, representan aze-
tidinilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, homopiperidinilo u homomorfolinilo, pudiendo estar cualquiera de dichos grupos sustituidos opcionalmente con uno o más sustituyentes.

Para uso en medicina, las sales de los compuestos de fórmula (I) serán sales farmacéuticamente aceptables. Sin embargo, otras sales pueden ser útiles en la preparación de los compuestos de la invención o de sus sales farmacéuticamente aceptables. Sales farmacéuticamente aceptables adecuadas de los compuestos de esta invención incluyen sales de adición de ácido que pueden, por ejemplo, formarse por mezcla de una solución del compuesto de la invención con una solución de un ácido farmacéuticamente aceptable tal como ácido clorhídrico, ácido sulfúrico, ácido metanosulfónico, ácido fumárico, ácido maleico, ácido succínico, ácido acético, ácido benzoico, ácido cítrico, ácido tartárico o ácido fosfórico. Adicionalmente, en los casos en que los compuestos de la invención llevan un resto ácido, v.g. carboxi, sales farmacéuticamente aceptables adecuadas de los mismos pueden incluir sales de metal alcalino, v.g. sales de sodio o potasio; sales de metal alcalinotérreo, v.g. sales de calcio o magnesio; y sales formadas con ligandos orgánicos adecuados, v.g. sales de amonio cuaternario.

La presente invención incluye dentro de su alcance solvatos de los compuestos de la fórmula (I) anterior. Tales solvatos pueden formarse con disolventes orgánicos comunes, v.g. disolventes hidrocarbonados tales como benceno o tolueno; disolventes clorados tales como cloroformo o diclorometano; disolventes alcohólicos tales como metanol, etanol o isopropanol; disolventes etéreos tales como dietil-éter o tetrahidrofurano; o disolventes de tipo éster tales como acetato de etilo. Alternativamente, los solvatos de los compuestos de fórmula (I) pueden formarse con agua, en cuyo caso los mismos serán hidratos.

Grupos alquilo adecuados que pueden estar presentes en los compuestos de la invención incluyen grupos alquilo

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C₁₋₆ de cadena lineal y ramificados, por ejemplo grupos alquilo C₁₋₄. Ejemplos típicos incluyen grupos metilo y etilo, y grupos propilo, butilo y pentilo de cadena lineal o ramificados. Grupos alquilo particulares incluyen metilo, etilo, *n*-propilo, isopropilo, *n*-butilo, sec-butilo, isobutilo, terc-butilo y 2,2-dimetilpropilo. Expresiones derivadas tales como "alcoxi C₁₋₆", "alquiltio C₁₋₆", "alquilsulfonilo C₁₋₆" y "alquilamino C₁₋₆" deben interpretarse en conformidad con lo anterior.

Grupos cicloalquilo C₃₋₇ específicos son ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y cicloheptilo.

Grupos arilo adecuados incluyen fenilo y naftilo, preferiblemente fenilo.

Grupos aril-alquilo (C₁₋₆) adecuados incluyen bencilo, feniletilo, fenilpropilo y naftilmetilo.

Grupos heterocicloalquilo adecuados, que pueden comprender análogos benzocondensados de los mismos incluyen azetidínilo, tetrahidrofuranilo, dioxolanilo, pirrolidinilo, indolinilo, imidazolidinilo, tetrahidropirranilo, piperidinilo, 1,2,3,4-tetrahydroquinolinilo, 1,2,3,4-tetrahydroisoquinolinilo, piperazinilo, morfolinilo y tiomorfolinilo.

Grupos heteroarilo adecuados incluyen grupos furilo, benzofurilo, dibenzofurilo, tienilo, benzotienilo, pirrolilo, indolilo, pirazolilo, indazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, imidazolilo, benzimidazolilo, oxadiazolilo, tiadiazolilo, triazolilo, tetrazolilo, piridinilo, quinolinilo, isoquinolinilo, piridazinilo, pirimidinilo y pirazinilo.

El término "halógeno", tal como se utiliza en esta memoria, tiene por objeto incluir átomos de flúor, cloro, bromo y yodo.

5 Cuando los compuestos de fórmula (I) tienen uno o más centros asimétricos, los mismos pueden existir de acuerdo con ello como enantiómeros. Cuando los compuestos de la invención poseen dos o más centros asimétricos, los mismos pueden existir adicionalmente como
10 diastereoisómeros. Debe entenderse que la invención se extiende a la totalidad de tales enantiómeros y diastereoisómeros, y a mezclas de los mismos en cualquier proporción, con inclusión de racematos. La fórmula (I) y las fórmulas representadas más adelante en esta memoria tienen por objeto representar todos los estereoisómeros individuales y todas las mezclas posibles de los mismos, a no ser que se establezca o se indique otra cosa. Adicionalmente, los compuestos de fórmula (I) pueden existir como tautómeros, por ejemplo tautómeros
15 ceto($\text{CH}_2\text{C}=\text{O}$)-enol ($\text{CH}=\text{CHOH}$). La fórmula (I) y las fórmulas representadas más adelante en esta memoria tienen por objeto representar la totalidad de los tautómeros individuales y todas las mezclas posibles de los mismos, a no ser que se indique o se exponga otra cosa.

25 En una realización, R^1 representa hidrógeno. En otra realización, R^1 representa halógeno, particularmente flúor o cloro, especialmente fluoro. En una realización adicional, R^1 representa alquilo C_{1-6} , especialmente metilo.

30 Típicamente, R^1 es fluoro.

En una realización, R^2 representa halógeno, especialmente bromo o yodo. En otra realización, R^2 representa alquilo C_{1-6} , especialmente metilo.

35 En una realización específica, R^2 es bromo. En otra realización específica, R^2 es yodo.

Convenientemente, R^a representa metilo o etilo, especialmente etilo.

Favorablemente, R^b representa hidrógeno; o alquilo C_{1-6} , cicloalquil C_{3-7} -alquilo(C_{1-6}), heterocicloalquil C_{3-7} o heterocicloalquil C_{3-7} -alquilo(C_{1-6}), pudiendo estar cualquiera de dichos grupos sustituido opcionalmente con uno o más sustituyentes.

Convenientemente, R^b representa hidrógeno; o alquilo C_{1-6} , arilo, aril-alquilo(C_{1-6}), heterocicloalquil C_{3-7} , heterocicloalquil C_{3-7} -alquilo(C_{1-6}), heteroarilo o heteroaril-alquilo(C_{1-6}), pudiendo estar cualquiera de dichos grupos sustituido opcionalmente con uno o más sustituyentes.

Convenientemente, el grupo R^b , o el resto cíclico $-NR^bR^c$, puede estar insustituido, o sustituido con uno o más sustituyentes, típicamente con uno o dos sustituyentes. En una realización, el grupo R^b , o el resto cíclico $-NR^bR^c$, está insustituido. En otra realización, el grupo R^b , o el resto cíclico $-NR^bR^c$, está monosustituido. En una realización adicional, el grupo R^b , o el resto cíclico $-NR^bR^c$, está disustituido.

Ejemplos de sustituyentes típicos en R^b , o en el resto cíclico $-NR^bR^c$, incluyen alquilo C_{1-6} , alcoxi C_{1-6} , hidroxil, hidroxil-alquilo(C_{1-6}), amino-alquilo(C_{1-6}), (amino)(hidroxil)-alquilo(C_{1-6}), halógeno, oxo, alquilcarbonilo C_{2-6} , carboxil, alcóxicarbonilo C_{2-6} , di-alquil(C_{1-6})-hidrazinilcarbonilo, amino, alquilamino C_{1-6} , di-alquilamino(C_{1-6}), alquilcarbonilamino C_{2-6} , aminocarbonilamino, aminocarbonilo, alquil C_{1-6} -aminocarbonilo, di-alquil(C_{1-6})aminocarbonilo, aminosulfonilo, alquilsulfonilo C_{1-6} y alquil C_{1-6} -aminocarbonilalquilo C_{1-6} . Ejemplos adicionales incluyen alcoxi C_{1-6} -alquilo(C_{1-6}), carboxil-alquilo(C_{1-6}), alcóxicarbonil C_{2-6} -alquilo(C_{1-6}), alcóxicarbonilamino C_{2-6} y alcóxicarbonilamino C_{2-6} -alquilo(C_{1-6}).

Ejemplos de sustituyentes particulares en R^b , o en el resto cíclico $-NR^bR^c$, incluyen metilo, metoxil, hidroxil, hidroximetilo, 2-hidroxietilo, aminometilo, 2-amino-3-hidroxipropilo, fluoro, oxo, acetilo, carboxil, metóxicarbonilo, etóxicarbonilo, terc-butoxicarbonilo,

dimetilhidrazinilcarbonilo, amino, metilamino, 1,3-dimetilbutilamino, dimetilamino, acetilamino, aminocarbonilamino, aminocarbonilo, etilaminocarbonilo, dietilaminocarbonilo, aminosulfonilo, metilsulfonilo y metilaminocarbonilmetilo. Ejemplos adicionales incluyen metoximetilo, carboximetilo, etoxycarbonilmetilo, terc-butoxicarbonilamino y terc-butoxicarbonilaminometilo.

Ejemplos de sustituyentes preferidos en R^b , o en el resto cíclico $-NR^bR^c$, incluyen alquilo C_{1-6} , alcoxi C_{1-6} -alquil(C_{1-6}), hidroxil, hidroxil-alquilo(C_{1-6}), amino, amino-alquilo(C_{1-6}), carboximetilo, alcoxycarbonilo C_{2-6} , alcoxycarbonil C_{2-6} -alquilo(C_{1-6}), di-alquilamino(C_{1-6}), alcoxycarbonilamino C_{2-6} y alcoxycarbonilamino C_{2-6} -alquilo(C_{1-6}).

Ejemplos de sustituyentes específicos en R^b , o en el resto cíclico $-NR^bR^c$, incluyen metilo, metoximetilo, hidroxil, hidroximetilo, 2-hidroxietilo, amino, aminometilo, carboximetilo, terc-butoxicarbonilo, etoxycarbonilmetilo, dimetilamino, terc-butoxicarbonilamino y terc-butoxicarbonilaminometilo.

Valores preferidos de R^b incluyen hidrógeno, metilo, etilo, propilo, ciclopropilmetilo, azetidino, pirrolidino, piperidino, azetidilmetilo, dioxolanilmetilo, pirrolidinilmetilo, morfoliniletilo y morfolinilpropilo, pudiendo estar cualquiera de dichos grupos sustituido opcionalmente con uno o más sustituyentes. Sustituyentes preferidos en este contexto incluyen alquilo C_{1-6} (especialmente metilo), hidroxil, amino, alcoxycarbonilo C_{2-6} (especialmente terc-butoxicarbonilo) y di-alquilamino (C_{1-6}) (especialmente dimetilamino).

Valores específicos de R^b incluyen hidrógeno, metilo, 2-hidroxietilo, 3-hidroxipropilo, 1-hidroxiprop-2-ilo, 2,3-dihidroxipropilo, 2-amino-2-metilpropilo, 2,2-dimetil-3-(dimetilamino)propilo, ciclopropilmetilo, 1-terc-butoxicarbonilazetidino-3-ilo, pirrolidino-3-ilo, 1-terc-butoxicarbonilpirrolidino-3-ilo, piperidino-3-ilo, piperidino-4-ilo, 1-metilpiperidino-4-ilo, 1-terc-

butoxycarbonilpiperidin-3-ilo, 1-terc-butoxi-
carbonil-piperidin-4-ilo, 1-terc-butoxycarbonil-
azetidin-3-ilmetilo, 2,2-dimetil-[1,3]dioxolan-4-
ilmetilo, pirrolidin-2-ilmetilo, 2-(morfolin-4-il)etilo
5 y 3-(morfolin-4-il)propilo.

Típicamente, R^b representa hidrógeno; o alquilo C_{1-6} ,
sustituido opcionalmente con uno o más, preferiblemente
uno o dos, grupos hidroxilo.

10 Valores típicos de R^b incluyen hidrógeno, metilo,
hidroxipropilo y dihidroxipropilo. En una realización,
 R^b representa hidrógeno. En otra realización, R^b repre-
senta metilo. En una realización adicional, R^b represen-
15 ta hidroxipropilo, especialmente 3-hidroxipropilo. En
una realización adicional, R^b representa dihidroxipropi-
lo, especialmente 2,3-dihidroxipropilo.

En una realización, R^c es hidrógeno. En otra realiza-
20 ción, R^c representa alquilo C_{1-6} , especialmente metilo.
En una realización adicional, R^c representa hidroxio-
alquilo(C_{1-6}), v.g. hidroxietilo (especialmente 2-
hidroxietilo).

25 Alternativamente, el resto $-NR^bR^c$ puede representar con-
venientemente azetidin-1-ilo, pirrolidin-1-ilo, piperi-
din-1-ilo, morfolin-4-ilo, tiomorfolin-4-ilo, piperaz-
in-1-ilo, homopiperidin-1-ilo u homomorfolin-4-ilo,
pudiendo estar cualquiera de dichos grupos sustituido
30 opcionalmente con uno o más sustituyentes. El resto $-
NR^bR^c$ puede representar también homopiperazin-1-ilo op-
cionalmente sustituido.

Valores particulares para el resto cíclico $-NR^bR^c$ inclu-
35 yen azetidin-1-ilo, pirrolidin-1-ilo, piperidin-1-ilo,
morfolin-4-ilo, piperazin-1-ilo y homopiperazin-1-ilo,
pudiendo estar cualquiera de dichos grupos sustituido
opcionalmente con uno o más sustituyentes.

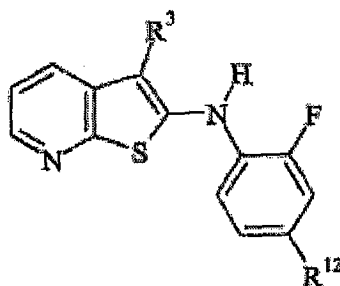
Valores específicos del resto cíclico $-NR^bR^c$ incluyen 3-hidroxiacetidin-1-ilo, 3-aminoacetidin-1-ilo, 3-(aminometilacetidin-1-ilo, 3-(*terc*-butoxicarbonil-amino)acetidin-1-ilo, 3-(*terc*-butoxicarbonilamino-metil)acetidin-1-ilo, pirrolidin-1-ilo, 2-(metoximetil)pirrolidin-1-ilo, 3-hidroxipirrolidin-1-ilo, 3-aminopirrolidin-1-ilo, 3-(*terc*-butoxicarbonil-amino)pirrolidin-1-ilo, 2-(hidroximetiliperidin-1-ilo, 4-aminopiperidin-1-ilo, 4-(*terc*-butoxicarbonil-amino)piperidin-1-ilo, morfolin-4-ilo, 2-(hidroximetil)morfolin-4-ilo, piperazin-1-ilo, 4-metilpiperazin-1-ilo, 2-(hidroximetil)-piperazin-1-ilo, 4-(2-hidroxietilpiperazin-1-ilo, 4-(carboximetilpiperazin-1-ilo, 4-(*terc*-butoxicarbonil)-2-(hidroximetilpiperazin-1-ilo, 4-(etoxicarbonilmetil)-piperazin-1-ilo y homopiperazin-1-ilo.

Convenientemente, el resto cíclico $-NR^bR^c$ puede estar sustituido con alquilo C_{1-6} , especialmente metilo. Valores particulares de $-NR^bR^c$ incluyen pirrolidin-1-ilo, morfolin-4-ilo, y 4-metilpiperazin-1-ilo.

Típicamente, R^3 representa ciano, $-CO_2R^a$, $-CONR^bR^c$, o $-CON(OR^b)R^c$, en donde R^a , R^b y R^c son como se define arriba. Convenientemente, R^3 representa ciano, $-CO_2R^a$ o $-CONR^bR^c$, especialmente ciano o $-CONR^bR^c$, en los cuales R^a , R^b y R^c son como se define arriba. Convenientemente, R^3 representa $-CON(OR^b)R^c$, en donde R^b y R^c son como se define arriba.

En una realización, R^3 representa ciano. En otra realización, R^3 representa $-CO_2R^a$, en donde R^a es como se define arriba. En una realización adicional, R^3 representa $-CONR^bR^c$, en donde R^b y R^c son como se define arriba. En una realización adicional, R^3 representa $-CON(OR^b)R^c$, en donde R^b y R^c son como se define arriba. En otra realización adicional, R^3 representa hidrógeno.

Un subgrupo particular de compuestos de acuerdo con la invención está representado por los compuestos de fórmula (II), y sales, solvatos y *N*-óxidos farmacéuticamente aceptables de los mismos:



(II)

en donde

R¹² representa halógeno; y

R³ es como se define arriba.

10

En una realización específica, R¹² es bromo. En otra realización específica R¹² es yodo.

15

Compuestos específicos nuevos de acuerdo con la presente invención incluyen cada uno de los compuestos cuya preparación se describe en los ejemplos que se acompañan, y sales y solvatos farmacéuticamente aceptables de los mismos.

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La presente invención proporciona también una composición farmacéutica que comprende un compuesto de fórmula (I) como se define arriba, o una sal, solvato o *N*-óxido farmacéuticamente aceptable del mismo, en asociación con uno o más vehículos farmacéuticamente aceptables.

25

Las composiciones farmacéuticas de acuerdo con la invención pueden presentar una forma conveniente para administración oral, bucal, parenteral, nasal, tópica, oftálmica o rectal, o una forma conveniente para administración por inhalación o insuflación.

30

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Para administración oral, las composiciones farmacéu-
cas pueden presentar la forma de, por ejemplo, table-
tas, pastillas o cápsulas preparadas por medios conven-
5 cionales con excipientes farmacéuticamente aceptables
tales como agentes aglomerantes (v.g. almidón de maíz
pregelatinizado, polivinilpirrolidona o hidroxipropil-
metil-celulosa); cargas (v.g. lactosa, celulosa micro-
cristalina o hidrogenofosfato de calcio); lubricantes
10 (v.g. estearato de magnesio, talco o sílice); desinte-
grantes (v.g. almidón de patata o glicolato de sodio);
o agentes humectantes (v.g. lauril-sulfato de sodio).
Las tabletas pueden estar recubiertas por métodos bien
conocidos en la técnica. Las preparaciones líquidas pa-
15 ra administración oral pueden presentar la forma de,
por ejemplo, soluciones, jarabes o suspensiones, o pue-
den presentarse como un producto seco para reconstitu-
ción con agua u otro vehículo adecuado antes de su uti-
lización. Tales preparaciones líquidas pueden prepararse
20 se por medios convencionales con aditivos farmacéutica-
mente aceptables tales como agentes de suspensión,
agentes emulsionantes, y vehículos o conservantes no
acuosos. Las preparaciones pueden contener también sa-
les tampón, agentes saborizantes, agentes colorantes, o
25 agentes edulcorantes, según sea apropiado.

Las preparaciones para administración oral pueden for-
mularse convenientemente para proporcionar una libera-
ción controlada del compuesto activo.

30 Para administración bucal, las composiciones pueden
presentar la forma de tabletas o pastillas formuladas
de manera convencional.

35 Los compuestos de fórmula (I) pueden formularse para
administración parenteral por inyección, v.g. por in-
yección de tipo bolus o infusión. Las formulaciones pa-
ra inyección pueden presentarse en forma de dosifica-

ción unitaria, v.g. en ampollas de vidrio o envases multi-dosis, v.g. viales de vidrio. Las composiciones para inyección pueden presentar formas tales como suspensiones, soluciones o emulsiones en vehículos aceitosos o acuosos, y pueden contener agentes de formulación tales como agentes de suspensión, estabilizadores, conservantes y/o dispersantes. Alternativamente, el ingrediente activo puede encontrarse en forma de polvo para constitución con un vehículo adecuado, v.g. agua estéril exenta de pirógenos, antes de su utilización.

Además de las formulaciones arriba descritas, los compuestos de fórmula (I) pueden formularse también como una preparación de tipo depósito. Tales formulaciones de acción prolongada pueden administrarse por implantación o por inyección intramuscular.

Para administración nasal o administración por inhalación, los compuestos de acuerdo con la presente invención pueden suministrarse convenientemente en la forma de una presentación de pulverización de tipo aerosol para envases presurizados o un nebulizador, con el uso de un propelente adecuado, v.g. diclorodifluorometano, fluorotriclorometano, diclorotetrafluoroetano, dióxido de carbono u otro gas o mezcla de gases adecuado(a).

Las composiciones pueden, en caso deseado, presentarse en un paquete o dispositivo dispensador que puede contener una o más formas de dosificación unitarias que contienen el ingrediente activo. El paquete o dispositivo dispensador puede ir acompañado de instrucciones para la administración.

Para administración tópica, los compuestos de acuerdo con la presente invención pueden formularse convenientemente en un ungüento adecuado que contiene el componente activo suspendido o disuelto en uno o más vehículos farmacéuticamente aceptables. Vehículos particula-

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res incluyen, por ejemplo, aceite mineral, petróleo líquido, propilenglicol, polioxietileno, polioxipropileno, cera emulsionante y agua. Alternativamente, los compuestos de acuerdo con la presente invención pueden formularse en una loción adecuada que contiene el componente activo suspendido o disuelto en uno o más vehículos farmacéuticamente aceptables. Vehículos particulares incluyen, por ejemplo, aceite mineral, monoestearato de sorbitán, polisorbato 60, cera de ésteres cetílicos, alcohol cetearílico, alcohol bencílico, 2-octildodecanol y agua.

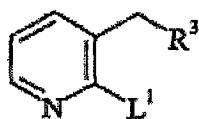
Para administración oftálmica, los compuestos de acuerdo con la presente invención pueden formularse convenientemente como suspensiones micronizadas en solución salina isotónica y estéril ajustada en pH, sea con o sin un conservante tal como un agente bactericida o fungicida, por ejemplo nitrato fenilmercúrico, cloruro de bencilalconio o acetato de clorhexidina. Alternativamente, para administración oftálmica los compuestos pueden formularse en un ungüento tal como petrolatum.

Para administración rectal, los compuestos de acuerdo con la presente invención pueden formularse convenientemente como supositorios. Éstos se pueden preparar por mezcla del componente activo con un excipiente adecuado no irritante que es sólido a la temperatura ambiente pero líquido a la temperatura rectal y por tanto fundirá en el recto para liberar el componente activo. Materiales de este tipo incluyen, por ejemplo, manteca de cacao, cera de abejas y polietilenglicoles.

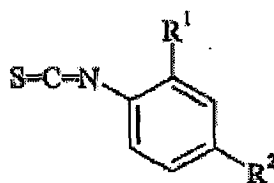
La cantidad de un compuesto de la invención requerida para la profilaxis o tratamiento de una afección particular variará dependiendo del compuesto seleccionado y del estado del paciente a tratar. En general, sin embargo, las dosis diarias pueden comprender desde aproximadamente 10 ng/kg a 1000 mg/kg, típicamente des-

de 100 ng/kg a 100 mg/kg, v.g. alrededor de 0,01 mg/kg a 40 mg/kg de peso corporal, para administración oral o bucal, desde aproximadamente 10 ng/kg a 50 mg/kg de peso corporal para administración parenteral, y desde alrededor de 0,05 mg a alrededor de 1000 mg, v.g. desde alrededor de 0,5 mg a alrededor de 1000 mg, para administración nasal o administración por inhalación o insuflación.

Los compuestos de fórmula (I) anteriores, y los N-óxidos de los mismos, se pueden preparar por un proceso que comprende hacer reaccionar un compuesto de fórmula (III) o un N-óxido del mismo, con un compuesto de fórmula (IV):



(III)



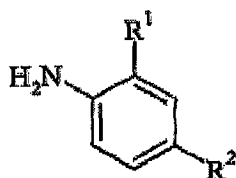
(IV)

en donde R¹, R² y R³ son como se define arriba, y L¹ representa un grupo lábil adecuado.

El grupo lábil L¹ es típicamente un átomo de halógeno, v.g. cloro.

La reacción se efectúa convenientemente, a una temperatura elevada en caso necesario, en un disolvente adecuado, v.g. dimetilsulfóxido, típicamente en condiciones básicas, v.g. en presencia de una base inorgánica tal como hidruro de sodio.

Los compuestos intermedios de la fórmula (IV) anterior se pueden preparar por reacción de un compuesto de fórmula (V):

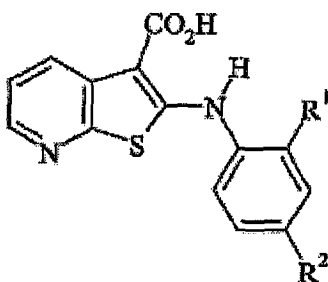


(V)

en donde R^1 y R^2 son como se define arriba, con tiofosgeno.

5 La reacción se efectúa convenientemente en un disolvente adecuado, típicamente una mezcla de cloroformo y agua.

10 En otro procedimiento, los compuestos de fórmula (I) anterior en donde R^3 representa $-\text{CONR}^b\text{R}^c$ o $-\text{CON}(\text{OR}^b)\text{R}^c$, y los *N*-óxidos de los mismos, se pueden preparar por un proceso que comprende hacer reaccionar un compuesto de fórmula $\text{H-NR}^b\text{R}^c$ o $\text{H-N}(\text{OR}^b)\text{R}^c$ con un compuesto de fórmula (VI), o un *N*-óxido del mismo:

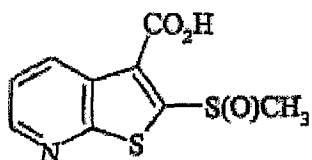


(VI)

15 en donde R^1 , R^2 , R^b y R^c son como se define arriba; en presencia de un agente de condensación.

20 Un agente de condensación adecuado es hidrocloruro de 1-(3-dimetilaminopropil)-3-carbodiimida (EDC), en cuyo caso la reacción se efectúa convenientemente en presencia de 1-hidroxibenzotriazol (HOBT) y *N*-metilmorfolina (NMM).

Los compuestos de fórmula (VI) anterior se pueden preparar por reacción del compuesto de fórmula (VII):



(VII)

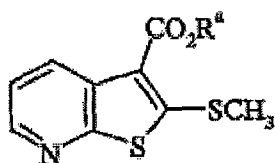
con un compuesto de fórmula (V) como se define arriba.

5

La reacción puede efectuarse convenientemente por tratamiento del compuesto (V) con una base, v.g. bis(trimetilsilil)amiduro de litio, en un disolvente adecuado, v.g. tetrahidrofurano, seguido por la adición del compuesto (VII).

10

El Compuesto Intermedio de fórmula (VII) anterior se puede preparar a partir de un compuesto de fórmula (VIII):



(VIII)

15

en donde R^a es como se define arriba; por saponificación del resto éster seguida por oxidación del grupo metilsulfanilo.

20

La saponificación del resto éster $-CO_2R^a$ en el compuesto (VIII) puede efectuarse por tratamiento con una base alcalina, v.g. hidróxido de sodio, en un disolvente adecuado, v.g. una mezcla acuosa de un alcohol inferior tal como metanol y un éter cíclico tal como tetrahidrofurano. La oxidación del grupo metilsulfanilo en el compuesto resultante puede efectuarse luego por tratamiento con un agente oxidante adecuado, v.g. Oxone® (pe-

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roximonosulfato de potasio), en un disolvente apropiado, v.g. metanol acuoso.

Los compuestos intermedios de la fórmula (VIII) anterior se pueden preparar por reacción de un compuesto de fórmula (III), en donde R^3 es $-CO_2R^a$ como se define arriba, con disulfuro de carbono, seguido por tratamiento con un haluro de metilo tal como yodometano.

La reacción se efectúa convenientemente en un disolvente adecuado, v.g. dimetilsulfóxido, en presencia de una base tal como hidruro de sodio.

En los casos en que no están disponibles comercialmente, los materiales de partida de fórmula (III) y (V) se pueden preparar por métodos análogos a los descritos en los ejemplos que se acompañan, o por métodos estándar bien conocidos en la técnica.

Se comprenderá que cualquier compuesto de fórmula (I) obtenido inicialmente por cualquiera de los procesos anteriores puede, en caso apropiado, elaborarse subsiguientemente para dar un compuesto ulterior de fórmula (I) por métodos bien conocidos en la técnica. A modo de ejemplo, un compuesto de fórmula (I) en la que R^3 representa $-CO_2R^a$ se puede convertir en el compuesto correspondiente en donde R^3 representa $-CONH_2$ por tratamiento con amoníaco, típicamente en un disolvente alcohólico inferior, v.g. etanol, a temperatura y presión elevadas. Alternativamente, un compuesto de fórmula (I) en donde R^3 representa $-CO_2R^a$ se puede convertir en el compuesto correspondiente en donde R^3 representa $-CONR^bR^c$ por tratamiento con la amina apropiada de fórmula $H-NR^bR^c$ en presencia de trimetilaluminio. Un compuesto de fórmula (I) en donde R^3 representa $-CO_2R^a$ se puede convertir en el compuesto correspondiente en donde R^3 representa hidrógeno por tratamiento con un reactivo alcalino tal como hidróxido de litio en condiciones forzadas, v.g.

por calentamiento a reflujo en una mezcla de etanol y agua. Un compuesto de fórmula (I) en donde R³ contiene un resto 2,2-dimetil-[1,3]dioxolan-4-ilmetilo se puede convertir en el compuesto correspondiente en donde R³ contiene un resto 2,3-dihidroxipropilo por tratamiento con un ácido mineral tal como ácido clorhídrico. Un compuesto de fórmula (I) en donde R³ contiene un átomo de nitrógeno al cual está unido un grupo terc-butoxicarbonilo (BOC) puede convertirse en el compuesto correspondiente en el que R³ contiene una funcionalidad N-H por tratamiento con un ácido, v.g. un ácido mineral tal como ácido clorhídrico, o un ácido orgánico tal como ácido trifluoroacético. Un compuesto de fórmula (I) en donde R³ contiene una funcionalidad N-H se puede convertir en el compuesto correspondiente en donde R³ contiene un átomo de nitrógeno al que está unido un grupo etoxycarbonilmetilo por tratamiento con cloroacetato de etilo, típicamente en presencia de trietilamina; el compuesto resultante puede convertirse luego en el compuesto correspondiente en donde R³ contiene un átomo de nitrógeno al cual está unido un grupo carboximetilo por tratamiento con un ácido alcalino tal como hidróxido de sodio, típicamente en una solución acuosa de un alcohol inferior tal como etanol. El derivado N-óxido de piridina de un compuesto de fórmula (I) se puede convertir en el compuesto correspondiente de fórmula (I) por tratamiento con trifenil-fosfina y tricloruro de fósforo.

En el caso en que se obtiene una mezcla de productos a partir de cualquiera de los procesos arriba descritos para la preparación de compuestos de acuerdo con la invención, el producto deseado puede separarse de aquélla en una etapa apropiada por métodos convencionales tales como HPLC preparativa; o cromatografía en columna utilizando, por ejemplo, sílice y/o alúmina en asociación con un sistema disolvente apropiado.

En donde los procesos arriba descritos para la preparación de los compuestos de acuerdo con la invención dan lugar a mezclas de estereoisómeros, estos isómeros se pueden separar por técnicas convencionales. En particular, donde se desea obtener un enantiómero particular de un compuesto de fórmula (I), éste puede producirse a partir de una mezcla correspondiente de enantiómeros utilizando cualquier procedimiento convencional adecuado para resolución de enantiómeros. Así, por ejemplo, los derivados diastereoisómeros, v.g. sales, pueden producirse por reacción de una mezcla de enantiómeros de fórmula (I), v.g. un racemato, y un compuesto quirral apropiado, v.g. una base quirral. Los diastereoisómeros pueden separarse luego por cualquier medio conveniente, por ejemplo por cristalización, y el enantiómero deseado puede recuperarse, v.g. por tratamiento con un ácido en el caso en que el diastereoisómero es una sal. En otro proceso de resolución, un racemato de fórmula (I) puede separarse utilizando HPLC quirral. Además, en caso deseado, puede obtenerse un enantiómero particular utilizando un Compuesto Intermedio quirral apropiado en uno de los procesos arriba descritos. Alternativamente, puede obtenerse un enantiómero particular por realización de una biotransformación enzimática específica de enantiómeros, v.g. una hidrólisis de ésteres utilizando una esterasa, y purificación posterior únicamente del ácido hidrolizado enantioméricamente puro a partir del éster antípoda que no ha reaccionado. Cromatografía, recristalización y otros procedimientos convencionales de separación pueden utilizarse también con compuestos intermedios o productos finales en los casos en que se desea obtener un isómero geométrico particular de la invención.

Durante cualquiera de las secuencias de síntesis anteriores puede ser necesario y/o deseable proteger grupos sensibles o reactivos en cualquiera de las moléculas de que se trate. Esto puede hacerse por medio de grupos

protectores convencionales, tales como los descritos en *Protective Groups in Organic Chemistry*, compilador J.F.W. McOmie, Plenum Press, 1973; y T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 3ª edición, 1999. Los grupos protectores pueden eliminarse en cualquier etapa conveniente posterior utilizando métodos conocidos en la técnica.

Los ejemplos que siguen ilustran la preparación de los compuestos de acuerdo con la invención.

Los compuestos de acuerdo con esta invención inhiben fuertemente la actividad de la enzima MEK humana.

Ensayo de MEK in vitro

Se midió la actividad de MEK 1 en un ensayo en cascada iniciado por Raf activo, por activación de MEK, Erk2 y fosforilación subsiguiente del sustrato Erk-tide marcado con fluoresceína en un ensayo basado en polarización de fluorescencia (IMAP). El ensayo se llevó a cabo en Tris 20 mM + MgCl₂ 5 mM + DL-ditiotreitol 2 mM + Tween 20 al 0,01%, de pH 7,2, que contenía MEK desactivada 1,5 nM, Erk desactivado 100 nM y Erk-tide 200 nM (todas las concentraciones son concentraciones finales). Los compuestos, o controles de DMSO, se sometieron a test a una concentración final de 2% DMSO, y el ensayo se inició en presencia de ATP 5 µM por adición de Raf activo 1,25 nM en tampón de ensayo. Después de 20 minutos a la temperatura ambiente, se añadió solución de parada seguida por perlas aglomerantes de IMAP, se incubó luego la mezcla de ensayo durante 90 min a la temperatura ambiente (con sacudidas) y se leyó después en un lector LJL HT de Molecular Devices.

Cuando se testaron en el ensayo anterior, se encontró que todos los compuestos de los ejemplos que se acompañan inhiben la enzima MEK humana con valores CI₅₀ de 10 µM o mejores.

EJEMPLOS***Abreviaturas utilizadas***

EtOAc - Acetato de etilo	DMSO - Dimetilsulfóxido
THF - Tetrahidrofurano	DCM - Diclorometano
Eter - dietiléter	CDCl ₃ - Deuterocloroformo
MeOH - Metanol	MeCN - Acetonitrilo
EtOH - Etanol	ES - Electropulverización
DMF - <i>N,N</i> -dimetilformamida	HOBT - 1-hidroxibenzotriazol
SiO ₂ - Sílice	NMM - <i>N</i> -metilmorfolina
h - hora(s)	min - minuto(s)
t.a. - temperatura ambiente	aq - acuoso
sat. - saturado	RT - tiempo de retención
BOC - <i>terc</i> -butoxicarbonilo	LiHMDS - bis(trimetilsilil)amiduro de litio
MCPBA - Ácido 3-cloroperoxibenzoico	
EDC - Hidrocloruro de 1-(3-dimetilaminopropil)-3-carbodiimida	

5 Todos los espectros NMR se obtuvieron a 300 MHz o 400 MHz.

10 Los compuestos se nombraron con ayuda de la Nomenclatura ACD Labs. (v. 7.0) suministrada por Advanced Chemical Development, Toronto, Canadá.

Método LCMS Estándar

15 El sistema LC-MS utilizado comprende un detector Waters Alliance 2795 HT HPLC cuaternario, un detector Waters 996 de red de fotodiodos (PDA) y un espectrómetro de masas de cuadripolo simple Waters ZQ 4000. El instrumento ZQ puede adquirir datos simultáneamente en modos de ionización por electropulverización positivo y negativo.

20

Espectrómetro de masas ZQ

Capilar	3,5 kV	Cono	50 V
Extractor	2 V	Temp. Fuente	80°C
Temp. de desolvatación	200°C	Gas de cono	150 l/h

Gas de desolvatación 250 l/h Multiplicador 650 V

Los datos se adquirieron en un barrido completo desde 100 a 1000 m/z.

Duración del barrido 0,80 s

5 Retardo interbarridos 0,20 s

HPLC

La separación analítica en fase inversa se realizó en un instrumento Gemini C18 de Phenomenex 50 x 4,6 mm con sílice de 5 µm.

Volumen de inyección 5 µl
Datos UV 240 a 400 nm
Temperatura de la muestra 20°C
Temperatura de la columna 30°C
Caudal 0,9 ml/min
División para ZQ ~0,40 ml/min

Disolvente A: 90% NH₄CO₂ 10 mM en agua/0,1% ácido fórmico/10% CH₃CN

Disolvente B: 90% CH₃CN/0,1% ácido fórmico/10% NH₄CO₂ 10 mM en agua

Disolvente C: 90% NH₄CO₂ 10 mM en agua/0,1% amoniaco/10% CH₃CN

Disolvente D: 90% CH₃CN/10% NH₄CO₂ 10 mM en agua/0,1% amoniaco

Programa de gradiente

Para el método 5_95_pH = 3

Tiempo (min)	A%	B%	Caudal	Curva
0,00	95,0	5,0	0,900	1
2,00	5,0	95,0	0,900	6
4,00	5,0	95,0	0,900	6
5,00	95,0	5,0	0,900	6

15

Para el método 5_95_pH = 10

Tiempo (min)	A%	B%	Caudal	Curva
0,00	95,0	5,0	0,900	1
2,00	5,0	95,0	0,900	6
4,00	5,0	95,0	0,900	6
5,00	95,0	5,0	0,900	6

UV-HPLC Preparativa

El sistema LC comprende una bomba cuaternaria Waters 2525, un detector de sistema de fotodiodos (PDA) Waters 996, un administrador de muestras Waters 2700, un organizador Fluidics Column y un colector de fracciones Waters que opera en fase inversa en uno de dos sistemas de pH.

Sistema de pH bajo (aproximadamente pH 3,2)

La separación en fase inversa se realizó en un instrumento Luna C18 de Phenomenex 100 x 21,2 mm con sílice de 5 µm.

Volumen de inyección	500 µl
Datos UV	254 nm
Caudal	20 ml/min
Disolvente A	90% agua/10% CH ₃ CN/0,1% ácido fórmico
Disolvente B	90% CH ₃ CN, 10% agua/0,1% ácido fórmico

Sistema de pH alto (aproximadamente pH 9,5)

La separación en fase inversa se llevó a cabo en un instrumento Gemini C18 de Phenomenex 150 x 21,2 mm con sílice de 10 µm.

Volumen de inyección	500 µl
Datos UV	254 nm
Caudal	20 ml/min
Disolvente C	90% NH ₄ HCO ₂ 10 mM en agua/0,1% amoníaco/10% CH ₃ CN
Disolvente D	90% CH ₃ CN/10% NH ₄ HCO ₂ 10 mM en agua/0,1% amoníaco

Perfiles de gradiente típicos se describen a continuación:

Programa de Gradiente para el Método de pH Bajo

Time	A%	B%	C%	D%	Flow	Curve
0.00	95.0	5.0	0.0	0.0	20	1
9.00	5.0	95.0	0.0	0.0	20	6
11.00	5.0	95.0	0.0	0.0	20	6
11.50	95.0	5.0	0.0	0.0	20	6
12.00	95.0	5.0	0.0	0.0	20	6

Gradient Program for High pH Method

Time	A%	B%	C%	D%	Flow	Curve
0.00	0.0	0.0	95.0	5.0	20	1
9.00	0.0	0.0	5.0	95.0	20	6
11.00	0.0	0.0	5.0	95.0	20	6
11.50	0.0	0.0	95.0	5.0	20	6
12.00	0.0	0.0	95.0	5.0	20	6

COMPUESTO INTERMEDIO 12-Fluoro-4-yodo-1-isotiocianatobenceno

Se añadió tiofosgeno (3,55 ml, 46,4 mmol) a una mezcla agitada rápidamente de 2-fluoro-4-yodoanilina (10,0 g, 42,2 mmol) en CHCl₃ (200 ml) y agua (100 ml). La mezcla se agitó a t.a. durante 16 h. La fase orgánica se secó (Na₂SO₄) y se concentró a vacío para dar el compuesto del título como un sólido cristalino blanquecino (11,8 g, cuantitativo). δ_H (DMSO-d₆) 7,87 (1H, dd, J = 1,8, 9,5 Hz), 7,63 (1H, ddd, J 1,0, 1,8, 8,4 Hz), 7,25 (1H, dd, J 8,2, 8,4 Hz).

COMPUESTO INTERMEDIO 22-[(4-Bromo-2-fluorofenil)amino]tieno[2,3-d]piridina-3-carboxilato de etilo

Se preparó a partir de (2-cloropiridina-3-il)acetato de etilo (D.H. Bremner et al., Synthesis, 1997, 949) (500

mg, 2,5 mmol) y 4-bromo-2-fluorofenil-isotiocianato (580 mg, 2,5 mmol) por el método del Ejemplo 1. El compuesto del título se obtuvo como un sólido blanquecino (390 mg, 40%). δ_H (DMSO- d_6) 10,37 (1H, br s), 8,25 (1H, dd, J 1,4, 8,1 Hz), 8,19 (1H, d, J 4,8 Hz), 7,69 (1H, dd, J 1,8, 10,2 Hz), 7,56-7,45 (2H, m), 7,32 (1H, dd, J 4,5, 8,1 Hz), 4,35 (2H, q, J 7,1 Hz), 1,37 (3H, t, J 7,1 Hz), LCMS (ES⁺) RT 4,66 minutos, 395 (M(⁷⁹Br)+H)⁺.

10 COMPUESTO INTERMEDIO 3

3-(terc-Butildimetilsilaniloxy)propilamina

A una solución de N-(3-hidroxipropil)ftalimida (5,25 g, 24,36 mmol) en DMF (20 ml) se añadió imidazol (16,6 g, 240 mmol) y cloruro de terc-butildimetilsililo (19 g, 120 mmol). La mezcla de reacción se agitó a la temperatura ambiente durante 18 horas antes de eliminar las materias volátiles a vacío y se sometió una porción del producto bruto a cromatografía en columna (SiO₂, 1:1 DCM/hexanos) para dar 2-[3-(terc-butildimetilsilaniloxy)propil]isoindol-1,3-diona como un aceite claro (5 g). Se disolvió 2-[3-(terc-butildimetilsilaniloxy)propil]isoindol-1,3-diona (5 g, 26,4 mmol) en etanol (50 ml) y se añadió metil-hidrazina (2,94 ml, 55,4 mmol). La mezcla de reacción se calentó a 75°C durante 8 horas antes de realizar la concentración a vacío. El residuo bruto se trituró con una mezcla de dietil-éter (150 ml) y hexanos (50 ml) y el sólido resultante se eliminó por filtración. Los disolventes se eliminaron a vacío para dar el compuesto del título como un aceite amarillo pálido (1,8 g, 61%). δ_H (DMSO- d_6) 4,58 (2H, br s), 3,63-3,58 (2H, m), 2,67-2,62 (2H, m), 1,60-1,55 (2H, m), 0,83 (9H, d, J 1,1 Hz), 0,00 (6H, d, J 1,2 Hz), LCMS (ES⁺) RT 1,77 minutos, 190 (M+H)⁺.

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COMPUESTO INTERMEDIO 4

Éster etílico del ácido 2-metilsulfaniltieno[2,3-b]piridina-3-carboxílico

A una solución de (2-cloropiridin-3-il)acetato de etilo (D.H. Bremner et al., Synthesis, 1997, 949) (8,0 g, 40,0 mmol) y disulfuro de carbono (3,18 g, 42,0 mmol) en DMSO (100 ml) se añadió hidruro de sodio en porciones (2,4 g, 60,0 mmol). Después de 60 minutos de agitación a la temperatura ambiente, la mezcla se calentó a 80°C durante 2 horas. Después de este tiempo, la mezcla de reacción se dejó enfriar a la temperatura ambiente y se añadió yoduro de metilo (7,6 g, 54,0 mmol). Después de 18 horas se añadió hielo (50 ml) y se formó un precipitado amarillo que se aisló por filtración para dar el compuesto del título como un sólido gris (7,95 g, 78%). δ_H (DMSO- d_6) 8,60 (1H, dd, J 1,6, 8,2 Hz), 8,46, (1H, dd, J 1,6, 4,6 Hz), 7,35 (1H, dd, J 4,6, 8,2 Hz), 4,48 (2H, q, J 7,1 Hz), 2,71, (3H, s), 1,49 (3H, t, J 7,1 Hz).

20 COMPUESTO INTERMEDIO 5

Ácido 2-metilsulfaniltieno[2,3-b]piridina-3-carboxílico
Una mezcla de Compuesto Intermedio 4 (12,5 g, 50,0 mmol) en THF (200 ml) y MeOH (50 ml) se trató con solución de hidróxido de sodio (solución al 10% en agua, 50 ml) y se agitó a la temperatura ambiente durante 18 h. Después de este tiempo, la mezcla de reacción se redujo a vacío a un tercio de su volumen. Se añadió luego agua (50 ml) antes de añadir HCl al 10% hasta que se formó un precipitado blanco. Se filtró éste para dar el compuesto del título como un sólido blanco cristalino (10.6 g, 95%). δ_H (DMSO- d_6) 13,50-13,20 (1H br s), 8,55 (1H, dd, J 1,2, 8,2 Hz), 8,48 (1H, dd, J 1,3, 4,5 Hz), 7,49 (1H, dd, J 4,6, 8,2 Hz), 3,25 (3H, s).

35 COMPUESTO INTERMEDIO 6

Ácido 2-metanosulfiniltieno[2,3-b]piridina-3-carboxílico

Se añadió oxona (14,5 g, 24,0 mmol) disuelta en agua (25 ml) a una mezcla agitada rápidamente de Compuesto Intermedio 5 (10,6 g, 47 mmol) en MeOH (250 ml). La mezcla se agitó a la temperatura ambiente durante 4 h. La mezcla de reacción se separó entre DCM (300 ml) y agua (200 ml). La capa orgánica se secó (Na₂SO₄) y se concentró a vacío para dar el compuesto del título como un sólido blanco cristalino (10,0 g, 88%). δ_H (DMSO-d₆) 14,20-13,80 (1H, br s), 8,73 (1H, dd, *J* 1,7, 8,3 Hz), 8,69 (1H, *J* 1,7, 4,6 Hz), 7,61 (1H, dd, *J* 4,6, 8,3 Hz), 3,05 (3H, s).

COMPUESTO INTERMEDIO 7

Ácido 2-[(2-fluoro-4-yodofenil)amino]tieno[2,3-b]piridina-2-carboxílico

A una solución agitada de 2-fluoro-4-yodoanilina (6,0 g, 25 mmol) en THF (100 ml) a 0°C (baño de hielo) se añadió LiHMDS (solución 1,0M en THF, 20,0 ml, 20,0 mmol) lentamente. La mezcla se dejó en agitación a la temperatura ambiente durante 30 minutos antes de enfriar a 0°C, y se añadió en porciones el Compuesto Intermedio 6 (2,00 g, 8,3 mmol). La mezcla se agitó a la temperatura ambiente durante 1 hora. Después de este tiempo, la mezcla de reacción se vertió en hielo y cuando se encontraba a la temperatura ambiente se añadió ácido cítrico hasta que se formó un precipitado. La mezcla se filtró para dar el compuesto del título como un sólido cristalino pardo claro (2,9 g, 84%). δ_H (DMSO-d₆) 14,00-13,00 (1H, br s), 10,80 (1H, s), 8,36 (1H, dd, *J* 1,3, 8,1 Hz), 8,32 (1H, dd, *J* 1,3, 4,8 Hz), 7,84 (1H, dd, *J* 1,8, 10,1 Hz), 7,69 (1H, d, *J* 8,3 Hz), 7,54 (1H, m), 7,42 (1H, dd, *J* 8,3, 4,8 Hz).

COMPUESTO INTERMEDIO 8

4-Yodo-1-isotiocianato-2-metilbenceno

A una solución en agitación de 4-yodo-2-metilanilina (1,0 g, 4,2 mmol) en DCM (50 ml) se añadió agua (20 ml) seguida por tiofosgeno (490 mg, 4,2 mmol). La mezcla de reacción se agitó durante una noche antes que se separaran las capas y la capa orgánica se secó (Na₂SO₄) y se evaporó a vacío para dar el producto deseado como un sólido pardo (1,05 g, 89%). δ_H (CDCl₃) 7,75 (1H, d, *J* 1,2 Hz), 7,62 (1H, dd, *J* 1,2, 8,3 Hz), 7,15 (1H, d, *J* 8,3 Hz), 2,20 (3H, s).

COMPUESTO INTERMEDIO 92-Cloro-4-yodo-1-isotiocianatobenceno

A una solución agitada de 2-cloro-4-yodoanilina (1,0 g, 3,9 mmol) en DCM (50 ml) se añadió agua (20 ml) seguida por tiofosgeno (476 mg, 4,1 mmol). La mezcla de reacción se agitó durante una noche antes que se separaran las capas y la capa orgánica se secó (Na₂SO₄) y se evaporó a vacío para dar el producto deseado como un sólido pardo (1,0 g, 86%). δ_H (CDCl₃) 7,79 (1H, d, *J* 1,9 Hz), 7,58 (1H, dd, *J* 1,9, 8,4 Hz), 6,97 (1H, d, *J* 8,4 Hz).

COMPUESTO INTERMEDIO 10Éster terc-butílico del ácido (2R)-2-[(2-[(2-fluoro-4-yodofenil)amino)tieno[2,3-b]piridina-3-carbonil)-amino)metil]pirrolidina-1-carboxílico

Se añadió hidrocloreuro de 1-(3-dimetilaminopropil)-3-carbodiimida (13,9 mg, 0,72 mmol) a una solución de Compuesto Intermedio 7 (150 mg, 0,36 mmol), 1-hidroxibenzotriazol (98 mg, 0,72 mmol), N-metilmorfolina (0,11 ml, 0,99 mmol) y (R)-2-(aminometil)-1-BOC-pirrolidina (144 mg, 0,72 mmol) en N,N-dimetilformamida (5 ml). La mezcla de reacción se agitó a t.a. durante 20 h, y se vertió luego en EtOAc (25 ml). La solución orgánica se lavó con salmuera sa-

ag 99

turada (3 x 25 ml), se secó (Na₂SO₄), se filtró y se concentró a vacío para dar un sólido pardo. El producto bruto se sometió a cromatografía en columna (SiO₂, 4:1 hexanos/EtOAc) para dar el compuesto del título, que se evaporó en éter para dar una espuma dura (135 mg, 63%).

5 δ_H (CDCl₃) 11,67 (1H, s), 8,35-8,33 (2H, m), 8,04 (1H, br s), 7,54-7,43 (3H, m), 7,32-7,30 (1H, m), 4,19 (1H, m), 3,82-3,78 (1H, m), 3,53-3,35 (3H, m), 2,18-1,86 (3H, m), 1,78 (1H, m), 1,45 (9H, s).

COMPUESTO INTERMEDIO 11

Éster terc-butílico del ácido (2S)-2-[(2-[(2-fluoro-4-yodofenil)amino]tieno[2,3-b]piridina-3-carbonil)-

15 amino)-metil]pirrolidina-1-carboxílico

Se preparó a partir del Compuesto Intermedio 7 (150 mg, 0,36 mmol), 1-hidroxibenzotriazol (98 mg, 0,78 mmol), N-metilmorfolina (0,11 ml, 0,99 mmol), hidrocloreuro de 1-(3-dimetilaminopropil)-3-carbodiimida (139 mg, 0,72 mmol) y (S)-2-(aminometil)-1-BOC-pirrolidina (144 mg, 0,72 mmol, por el método del Compuesto Intermedio 10. El compuesto del título se evaporó en éter para dar una espuma incolora dura (139 mg, 64%).

20 δ_H (CDCl₃) 11,67 (1H, s), 8,35-8,33 (2H, m), 8,04 (1H, br s), 7,54-7,43 (3H, m), 7,32-7,30 (1H, m), 4,19 (1H, m), 3,82-3,78 (1H, m), 3,53-3,35 (3H, m), 2,18-1,86 (3H, m), 1,78 (1H, m), 1,45 (9H, s).

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COMPUESTO INTERMEDIO 12

30 Ácido (2-cloropiridin-3-il)acético

Se calentó a reflujo 2-cloro-3-(cianometil)piridina (D.H. Bremner et al., Synthesis, 1997, 949) (10,3 g, 67,1 mmol) en HCl concentrado (100 ml) durante 3 h. La mezcla de reacción se concentró a vacío y el residuo se suspendió en agua. El sólido blanco se recrystalizó por filtración y se lavó con agua, después de lo cual se secó a vacío proporcionando el producto requerido

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(11,15 g). δ_H (DMSO- d_6) 12,60 (1H, br s), 8,32 (1H, dd, J 4,7, 1,9 Hz), 7,86 (1H, dd, J 7,5, 1,9 Hz), 7,40 (1H, dd, J 7,5, 4,7 Hz), 3,75 (2H, s), LCMS (ES⁺) RT 1,85 minutos, 174 (M+H)⁺.

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COMPUESTO INTERMEDIO 13

Éster metílico del ácido (2-cloropiridin-3-il)acético

A una suspensión del Compuesto Intermedio 12 (3,88 g, 22,6 mmol) en metanol se añadió cloruro de acetilo (1,8 ml, 24,9 mmol) y la mezcla se calentó a 70°C durante 18 horas. Se eliminaron los disolventes a vacío para dar el compuesto del título como un aceite pardo claro (4,63 g, cuantitativo). δ_H (DMSO- d_6) 8,35 (1H, dd, J 4,7, 1,9 Hz), 7,88 (1H, dd, J 8,5, 1,9 Hz), 7,43 (1H, dd, J 8,5, 4,7 Hz), 3,80 (2H, s), 3,65 (3H, s), LCMS (ES⁺) RT 2,40 minutos, 186 (M+H)⁺.

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COMPUESTO INTERMEDIO 14

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Éster metílico del ácido 2-[(2-fluoro-4-yodofenil)-amino]tieno[2,3-*b*]piridina-3-carboxílico

A una solución del Compuesto Intermedio 13 (4,1 g, 22,1 mmol) y Compuesto Intermedio 1 (6,16 g, 22,1 mmol) en DMSO seco bajo nitrógeno se añadió hidruro de sodio (1,05 g, 24,3 mmol, dispersión al 60% en peso en aceite mineral). La mezcla se agitó a la temperatura ambiente durante 15 minutos y se calentó luego a 90°C durante 3 horas. Se enfrió la mezcla de reacción, y se vertió luego sobre agua con hielo (200 ml). La fase acuosa se extrajo con EtOAc (3 x 200 ml), se lavaron los extractos orgánicos combinados con salmuera, se secaron (MgSO₄), se filtraron y se eliminaron los disolventes a vacío. El sólido amarillo pegajoso se trituró con etanol para dar un sólido amarillo fino que se recogió por filtración, se lavó con dietil-éter y se secó bajo succión para dar el compuesto del título como un sólido amarillo pálido (1,73 g). δ_H (DMSO- d_6) 10,30 (1H, s),

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8,36-8,31 (2H, m), 7,87 (1H, dd, J 1,9, 10,0 Hz), 7,70 (1H, d, J 6,6 Hz), 7,51 (1H, t, J 8,5 Hz), 7,42 (1H, dd, J 5,7, 8,1 Hz), 3,94 (3H, s), LCMS (ES⁺) RT 4,00 minutos, 429 (M+H)⁺.

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COMPUESTO INTERMEDIO 15

2-(2-Cloropiridin-3-il)-N-metoxi-N-metilacetamida

El Compuesto Intermedio 12 (500 mg, 2,9 mmol) en dicloroetano (20 ml) con *N,O*-dimetilhidroxilamina (300 mg, 3,04 mmol), EDC (583 mg, 3,04 mmol) y *N*-metil-morfolina (0,98 ml, 8,70 mmol) se agitaron a t.a. durante 18 h. La mezcla de reacción se lavó con HCl 2M, y la fase orgánica se secó (sulfato de magnesio) y se concentró a vacío. La cromatografía (SiO₂; 1:1 acetato de etilo:DCM) proporcionó el compuesto del título (320 mg) como un sólido blanco. δ_H (DMSO-d₆) 8,31 (1H, dd, J 4,7, 1,9 Hz), 7,81 (1H, dd, J 7,5, 1,9 Hz), 7,40 (1H, dd, J 7,5, 4,7 Hz), 3,93 (2H, s), 3,76 (3H, s), 3,15 (3H, s), LCMS (ES⁺) RT 2,22 minutos, 215/217 (M+H)⁺.

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COMPUESTO INTERMEDIO 16

2-(2-Cloro-1-oxipiridin-3-il)-N-metoxi-N-metilacetamida

El Compuesto Intermedio 15 (270 mg, 1,25 mmol) se disolvió en DCM (5 ml) y se trató con mCPBA (324 mg, 1,88 mmol). Después de agitar a t.a. durante 3 días, la mezcla de reacción se vertió directamente en una columna flash y se cromatografió (SiO₂; acetato de etilo → 5% metanol en acetato de etilo), proporcionando el producto requerido (265 mg), como un sólido blanco. δ_H (DMSO-d₆) 8,39 (1H, dd, J 5,4, 2,5 Hz), 7,37-7,35 (2H, m), 3,98 (2H, s), 3,76 (3H, s), 3,15 (3H, s), LCMS (ES⁺) RT 1,81 minutos, 231/233 (M+H)⁺.

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EJEMPLO 12-[(2-Fluoro-4-yodofenil)amino]tieno[2,3-b]piridina-3-carboxilato de etilo

5 Se añadió en porciones hidruro de sodio (650 mg de una dispersión al 60% en aceite mineral, 16,2 mmol) durante 10 min a una mezcla del Compuesto Intermedio 1 (3,75 g, 13,5 mmol) y (2-cloropiridin-3-il)acetato de etilo (D.H. Bremner et al., Synthesis, 1997, 949) (2,7 g, 13,5 mmol) en DMSO (25 ml). Cuando hubo cesado el desprendimiento de gas, la mezcla se calentó a 70°C durante 3 h y se dejó luego a t.a. durante una noche. Se añadió agua (150 ml) y se decantó el líquido del sólido resultante. La masa sólida se trató con etanol (40 ml) para dar una suspensión fina de color blanco que se separó por filtración, se lavó con etanol (10 ml) y éter (2 x 15 ml) y se secó a vacío a 40°C para dar el compuesto del título como un sólido blanco (2,90 g, 48%). δ_H (DMSO- d_6) 10,40 (1H, s), 8,40-8,30 (2H, m), 7,85 (1H, dd, J 1,9, 10,1 Hz), 7,70 (1H, d, J 8,5 Hz), 7,55-7,49 (1H, m), 7,43 (1H, dd, J 4,9, 8,0 Hz), 4,43 (2H, q, J 7,9 Hz), 1,41 (3H, t, J 7,9 Hz), LCMS (ES^+) RT 5,27 minutos, 443 ($M+H$) $^+$.

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EJEMPLO 22-[(2-Fluoro-4-yodofenil)amino]-N-metiltieno[2,3-b]piridina-3-carboxamida

30 Se añadió trimetilaluminio (1,5 ml de una solución 2M en hexano, 3,0 mmol) a una solución de metilamina (1,5 ml de una solución 2M en THF, 3,0 mmol) en tolueno (5 ml). Después de 5 min, se añadió el Ejemplo 1 (250 mg, 0,60 mmol) y la mezcla se calentó a 100°C durante 4 h. Después de enfriar, la mezcla de reacción se extinguió con solución saturada de cloruro de amonio (75 ml) y HCl (10 ml, 2M) y se extrajo luego con EtOAc (80 ml). La fase orgánica se secó (Na_2SO_4) y se concentró a vacío para dar un sólido. La tritución con éter (30 ml) y

filtración dieron el compuesto del título como un sólido blanquecino (138 mg, 57%). δ_H (CDCl₃) 11,13 (1H, br s), 8,25 (1H, dd, J 1,4, 4,7 Hz), 7,80 (1H, dd, J 1,4, 8,2 Hz), 7,46-7,42 (2H, m), 7,33 (1H, dd, J 8,3, 8,3 Hz), 7,21 (1H, dd, J 4,7, 8,2 Hz), 5,82 (1H, br s), 3,00 (3H, d, J 4,8 Hz), LCMS (ES⁻) RT 3,63 minutos, 426 (M-H)⁻.

EJEMPLO 3

2-[(2-Fluoro-4-yodofenil)amino]-N,N-dimetiltieno[2,3-b]piridina-3-carboxamida

Se preparó a partir del Ejemplo 1 (100 mg, 0,23 mmol) y dimetilamina (0,35 ml de una solución 2,0M en THF, 0,7 mmol) por el método del Ejemplo 2. El compuesto del título se obtuvo como un sólido blanco (21 mg, 20%). δ_H (DMSO-d₆) 9,12 (1H, s), 8,35 (1H, dd, J 1,6, 4,7 Hz), 7,77 (1H, dd, J 1,6, 8,1 Hz), 7,67 (1H, dd, J 1,9, 10,6 Hz), 7,48 (1H, dd, J 1,1, 1,9 Hz), 7,35 (1H, dd, J 4,7, 8,0 Hz), 7,15-7,10 (1H, m), 2,87 (6H, s), LCMS (ES⁺) RT 3,29 minutos, 442 (M+H)⁺.

EJEMPLO 4

N-(2-Fluoro-4-yodofenil)-3-(morfolin-4-ilcarbonil)-tieno[2,3-b]piridin-2-amina

Se preparó a partir del Ejemplo 1 (250 mg, 0,60 mmol) y morfolina (0,26 ml, 3 mmol) por el método del Ejemplo 2. Se obtuvo el compuesto del título como un sólido blanco (215 mg, 78%). δ_H (DMSO-d₆) 9,22 (1H, br s), 8,34 (1H, dd, J 1,4, 4,6 Hz), 7,81 (1H, dd, J 1,4, 8,0 Hz), 7,68 (1H, dd, J 1,9, 10,5 Hz), 7,50-7,46 (1H, m), 7,35 (1H, dd, J 4,6, 8,0 Hz), 7,13 (1H, dd, J 8,6, 8,6 Hz), 3,54-3,48 (4H, m), 3,43-3,39 (4H, m), LCMS (ES⁺) RT 3,17 minutos, 484 (M+H)⁺.

EJEMPLO 5

N-(2-Fluoro-4-yodofenil)-3-[(4-metilpiperazin-1-il)-carbonil]tieno[2,3-b]piridin-2-amina

5 Se añadió trimetilaluminio (1,5 ml de una solución 2M en hexano, 3,0 mmol) a una solución de 1-metilpiperazina (0,333 ml, 3,0 mmol) en tolueno (5 ml). Después de 10 min, se añadieron el Ejemplo 1 (250 mg, 0,60 mmol) y tolueno (2 ml) y la mezcla se calentó a 10 90°C durante 6 h. Después de enfriar, se extinguió la mezcla con NaOH (50 ml, 1M) y se extrajo con EtOAc (50 ml más 25 ml). Los extractos orgánicos combinados se lavaron con salmuera saturada (50 ml), se secaron (Na₂SO₄) y se concentraron a vacío para dar un sólido 15 amarillo. La trituration con hexano/éter (10:1, 30 ml) y filtración dieron el compuesto del título como un sólido amarillo pálido (245 mg, 87%). δ_H (DMSO-d₆) 9,13 (1H, br s), 8,37 (1H, br d, J 4,4 Hz), 7,79 (1H, br d, J 7,8 Hz), 7,67 (1H, br d, J 10,4 Hz), 7,47 (1H, br d, J 8,4 Hz), 7,37 (1H-1, dd, J 4,7, 8,1 Hz), 7,10 (1H, m), 3,30 (4H, br s), 2,21 (4H, br s), 2,14 (3H, s), LCMS (ES) RT 2,09 minutos, 497 (M+H)⁺.

EJEMPLO 6

25 2-[(4-Bromo-2-fluorofenil)amino]-N-(2,3-dihidroxi-propil)tieno[2,3-b]piridina-3-carboxamida

Se añadió trimetilaluminio (0,95 ml de una solución 2M en hexano, 1,90 mmol) a una solución de 2,2-dimetil-1,3-dioxolano-4-metanamina (249 mg, 1,9 mmol) en tolueno (4 ml). Después de 2 minutos, se añadió el Compuesto Intermedio 2 (150 mg, 0,38 mmol) y la mezcla se calentó a 90°C durante 4 h. Después de enfriar, la mezcla de reacción se extinguió con solución saturada de cloruro de amonio (5 ml) y HCl (5 ml, 2M), se agitó, y se extrajo luego con EtOAc (2 x 25 ml) y DCM (25 ml). Se secó la fase orgánica (Na₂SO₄) y se concentró a vacío para dar un sólido. La trituration con éter/hexano (1:3, 10 35

ml) y filtración dieron el compuesto del título como un sólido blanco (95 mg, 57%). δ_H (DMSO- d_6) 10,64 (1H, br s), 8,36 (1H, dd, J 1,4, 4,7 Hz), 8,20 (1H, dd, J 1,4, 8,2 Hz), 7,89 (1H, dd, J 8,8, 8,8 Hz), 7,69 (1H, dd, J 2,1, 10,6 Hz), 7,58 (1H, dd, J 8,8, 8,8 Hz), 7,48-7,41 (2H, m), 4,86 (1H, d, J 5,0 Hz), 4,64 (1H, t, J 5,7 Hz), 3,72-3,66 (1H, m), 3,52-3,36 (3H, m), 3,31-3,22 (1H, m), LCMS (ES⁺) RT 2,80 minutos, 440 (M(⁷⁹Br)+H)⁺.

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EJEMPLO 72-[(2-Fluoro-4-yodofenil)amino]-N-(2,3-dihidroxi-propil)tieno[2,3-b]piridina-3-carboxamida

Se preparó a partir del Ejemplo 1 (150 mg, 0,34 mmol) y 2,2-dimetil-1,3-dioxolano-4-metanamina (0,14 ml, 1,0 mmol) por el método del Ejemplo 6. Se obtuvo el compuesto del título como un sólido amarillo pálido (94 mg, 57%). δ_H (DMSO- d_6) 10,68 (1H, s), 8,36-8,35 (1H, m), 8,20 (1H, dd, J 1,2, 8,2 Hz), 7,90-7,87 (1H, m), 7,76 (1H, dd, J 1,7, 10,4 Hz), 7,62-7,59 (1H, m), 7,45-7,40 (2H, m), 4,86 (1H, d, J 5,0 Hz), 4,64 (1H, t, J 5,7 Hz), 3,72-3,64 (1H, m), 3,51-3,41 (3H, m), 3,40-3,34 (1H, m), LCMS (ES⁺) RT 2,91 minutos, 488 (M+H)⁺.

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EJEMPLO 82-[(2-Fluoro-4-yodofenil)amino]tieno[2,3-b]piridina-3-carboxilato-7-óxido de etilo

Se preparó a partir del Compuesto Intermedio 1 (2,38 g, 8,58 mmol) y (2-cloro-1-oxidopiridin-3-il)acetato de etilo (D.H. Bremner, et al., Synthesis, 1997, 949) (1,85 g, 8,58 mmol) por el método del Ejemplo 1. Se obtuvo el compuesto del título como un sólido amarillo pálido (3,10 g, 79%). δ_H (DMSO- d_6) 10,31 (1H, br s), 8,20 (1H, d, J 5,9 Hz), 7,94 (1H, d, J 7,8 Hz), 7,89 (1H, dd, J 1,8, 10,0 Hz), 7,72 (1H, d, J 8,4 Hz), 7,55-7,46 (2H, m), 4,41 (2H, q, J 8,4 Hz), 1,40 (3H, t, J 7,1 Hz), LCMS (ES⁺) RT 3,44 minutos, 459 (M+H)⁺.

EJEMPLO 9

5 N-2,3-Dihidroxiopropil)-2-[(2-fluoro-4-yodofenil)amino]-
tieno[2,3-b]piridina-3-carboxamida-7-óxido

Se preparó a partir del Ejemplo 8 (200 mg, 0,43 mmol) y
2,2-dimetil-1,3-dioxolano-4-metanamina (0,18 ml, 1,3
mmol) por el método del Ejemplo 6. Se obtuvo el com-
puesto del título como un sólido blanco mg, 15%). δ_H
10 (DMSO- d_6) 10,60 (1H, s), 8,22 (1H-1, m), 7,90 (1H, s),
7,84-7,76 (2H, m), 7,64-7,60 (1H, m), 7,45-7,40 (2H,
m), 4,78 (1H-1, d, J 4,9 Hz), 4,64 (1H, t, J 5,6 Hz),
3,70-3,60 (1H, m), 3,50-3,15 (4H, m), LCMS (ES) RT 2,37
minutos, 502 (M-H)⁻.

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EJEMPLO 10

2-[(2-Fluoro-4-yodofenil)amino]tieno[2,3-b]piridina-3-
carbonitrilo

20 A una solución de (2-cloropiridin-3-il)acetonitrilo
(D.H. Bremner et al., Synthesis, 1997, 949) (700 mg,
4,59 mmol) y Compuesto Intermedio 1 (1,28 g, 4,60 mmol)
en DMSO seco (15 ml) se añadió hidruro de sodio (202
mg, 60% en aceite mineral, 5,06 mmol). La mezcla se
25 agitó a la temperatura ambiente durante 15 minutos an-
tes de calentarla a 90°C durante 4 horas. La mezcla de
reacción se vertió en agua (80 ml) y el sólido precipi-
tado se filtró y se lavó con agua/etanol (mezcla 2:1,
50 ml) seguido por dietil-éter/hexano (mezcla 1:1, 20
30 ml). El sólido se secó en un horno de vacío y se re-
cristalizó en etanol/agua para proporcionar el compues-
to del título como un sólido pardo claro. (800 mg,
45%). δ_H (DMSO- d_6) 10,40 (1H, s), 8,37 (1H, dd, J 1,3,
4,6 Hz), 7,83-7,81 (2H, m), 7,64 (1H, d, J
35 8,3 Hz), 7,44 (1H, dd, J 4,7, 8,0 Hz), 7,33 (1H, dd, J
8,3, 8,3 Hz), LCMS RT 3,08 minutos, (ES⁻) 394 (M-H)⁻,
(ES⁺) 396 (M+H)⁺.

EJEMPLO 11

Amida del ácido 2-[(2-fluoro-4-yodofenil)amino]tieno-
[2,3-b]piridina-3-ácido carboxílico

- 5 Una solución del Ejemplo 1 (250 mg, 0,56 mmol) en etanol (5 ml) se añadió a amoniaco líquido (15 ml) y la mezcla se calentó en un aparato Parr a 95°C y a 800 psi (54,4 atm) durante 18 horas. Las materias volátiles se eliminaron a vacío para dar un residuo aceitoso pardo.
- 10 La trituration repetida con etanol y DCM proporcionó el compuesto del título como un sólido blanco (18 mg) δ_H (DMSO- d_6) 11,20 (1H, bs), 8,34 (1H, d, J 3,4 Hz), 8,20 (1H, dd, J 8,2, 1,3 Hz), 7,76 (1H, dd, J 10,4, 1,8 Hz), 7,62 (1H, d, J 8,2 Hz), 7,57 (2H, br s), 7,49-7,39 (2H, m), LCMS (ES⁺) RT 3,11 minutos, 412 (M+H)⁺.
- 15

EJEMPLO 12

[2-[(2-Fluoro-4-yodofenil)amino]tieno[2,3-b]piridin-3-il](pirrolidin-1-il)metanona

- 20 Preparada a partir del Ejemplo 1 (250 mg, 0,60 mmol) y pirrolidina (0,25 ml, 3 mmol) por el método del Ejemplo 2. Se obtuvo el compuesto del título como un sólido amarillo pálido (136 mg, 51%). δ_H (DMSO- d_6) 9,21 (1H, br s), 8,35 (1H, dd, J 1,6, 4,7 Hz), 7,81 (1H, dd, J 1,6, 8,1 Hz), 7,67 (1H, dd, J 1,9, 10,5 Hz), 7,50-7,46 (1H, m), 7,35 (1H, dd, J 4,7, 8,1 Hz), 7,13 (1H, dd, J 8,6, 8,6 Hz), 3,32-3,30 (4H, m), 1,78-1,73 (4H, m), LCMS (ES⁺) RT 3,32 minutos, 468 (M+H)⁺.
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- 30

EJEMPLO 13

(3-Hidroxipropil)amida del ácido 2-[(2-fluoro-4-yodofenil)amino]tieno[2,3-b]piridina-3-carboxílico

- 35 Se disolvió el Ejemplo 1 (500 mg, 1,13 mmol) en tolueno seco (6 ml) bajo nitrógeno. Se añadió a esta solución trimetilaluminio (2,83 ml de una solución 2M en hexano, 5,66 mmol) durante 5 minutos. Después de 10 minutos, se

añadió una solución del Compuesto Intermedio 3 (1,07 g, 5,66 mmol) en tolueno seco (5 ml) y la mezcla de reacción se calentó a 100°C durante 6 horas. Se dejó enfriar la mezcla de reacción a la temperatura ambiente y se trató con HCl 2M (10 ml) y agua (30 ml). La mezcla se extrajo con acetato de etilo (3 x 50 ml), se secaron luego las fases orgánicas sobre Na₂SO₄ y se filtraron, después de lo cual se eliminaron los disolventes a vacío. El residuo bruto se disolvió en metanol (30 ml), se trató con HCl 2M (20 ml) y se agitó a la temperatura ambiente durante 18 horas. La mezcla se concentró a vacío, se trató con NaOH 2M (20 ml) y se extrajo con acetato de etilo (3 x 50 ml). Las fases orgánicas se secaron sobre Na₂SO₄, se filtraron, y se eliminaron las materias volátiles a vacío. El sólido residual se trituró con dietil-éter (10 ml) y se secó en un horno de vacío para dar el compuesto del título como un sólido amarillo pálido (100 mg, 19%). δ_H (DMSO-d₆) 10,75 (1H, br s), 8,35 (1H, m), 8,17 (1H, d, *J* 7,9 Hz), 8,01 (1H, br s), 7,75 (1H, d, *J* 10,1 Hz), 7,59 (1H, d, *J* 8,1 Hz), 7,44-7,41 (2H, m), 4,55 (1H, t, *J* 5,1 Hz), 3,54-3,48 (2H, m), 3,41-3,34 (2H, m), 1,75-1,67 (2H, m), LCMS (ES⁺) RT 3,22 minutos, 472 (M+H)⁺.

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EJEMPLO 14

(2(S),3-Dihidroxiopropil)amida del ácido 2-[(2-fluoro-4-yodofenil)amino]tieno[2,3-b]piridina-3-carboxílico
Preparada a partir del Ejemplo 1 (1,0 g, 2,26 mmol) y (S)-(2,2-dimetil-1,3-dioxolan-4-il)metilamina (1,48 g, 11,3 mmol) por el método del Ejemplo 6. Se obtuvo el compuesto del título como un sólido blanco (425 mg, 39%). δ_H (DMSO-d₆) 10,67 (1H, bs), 8,36 (1H, d, *J* 3,8 Hz), 8,20 (1H, d, *J* 8,5 Hz), 7,88 (1H, bs), 7,76 (1H, d, *J* 10,5 Hz), 7,61 (1H, d, *J* 8,5 Hz), 7,46-7,40 (2H, m), 4,86 (1H, d, *J* 5,0 Hz), 4,64 (1H, t, *J* 5,7 Hz), 3,72-3,67 (1H, m), 3,52-3,38 (3H, m), 3,30-3,22 (1H, m), LCMS (ES⁺) RT 2,91 minutos, 488 (M+H)⁺.

EJEMPLO 15

(2(R),3-Dihidroxipropil)amida del ácido 2-[(2-fluoro-4-yodofenil)amino]tieno[2,3-b]piridina-3-carboxílico

Preparada a partir del Ejemplo 1 (500 mg, 1,13 mmol) y (R)-(2,2-dimetil-1,3-dioxolan-4-il)metilamina (655 g, 4,52 mmol) por el método del Ejemplo 6. Se obtuvo el compuesto del título como un sólido blanco (100 mg, 18%). δ_H (DMSO- d_6) 10,67 (1H, bs), 8,36 (1H, d, J 3,8 Hz), 8,20 (1H, d, J 8,5 Hz), 7,88 (1H, bs), 7,76 (1H, d, J 10,5 Hz), 7,61 (1H, d, J 8,5 Hz), 7,46-7,40 (2H, m), 4,86 (1H, d, J 5,0 Hz), 4,64 (1H, t, J 5,7 Hz), 3,72-3,67 (1H, m), 3,52-3,38 (3H, m), 3,30-3,22 (1H, m), LCMS (ES⁺) RT 2,91 minutos, 488 (M+H)⁺.

EJEMPLO 16

Metilamida del ácido 2-[(4-bromo-2-fluorofenil)amino]tieno[2,3-b]piridina-3-carboxílico

Preparada a partir del Compuesto Intermedio 2 (150 mg, 0,38 mmol) y una solución 2M de metilamina en THF (0,95 ml, 1,9 mmol) por el método del Ejemplo 2. Se obtuvo el compuesto del título como un sólido blanco (125 mg, 87%). δ_H (DMSO- d_6) 10,83 (1H, bs), 8,35 (1H, dd, J 1,4, 4,6 Hz), 8,18 (1H, dd, J 1,4, 8,2 Hz), 7,92 (1H, bs), 7,69 (1H, dd, J 2,1, 10,6 Hz), 7,59 (1H, dd, J 8,8, 8,8 Hz), 7,48-7,43 (1H, m), 7,42 (1H, dd, J 8,2, 4,6 Hz), 2,83 (3H, d, J 4,5 Hz), LCMS (ES⁺) RT 3,45 minutos, 380/382 [Br⁷⁹/Br⁸¹] (M+H)⁺.

EJEMPLO 17

Éster etílico del ácido 2-[(4-yodofenil)amino]tieno[2,3-b]piridina-3-carboxílico

Se preparó a partir de (2-cloropiridin-3-il)acetato de etilo (D.H. Bremner et al., Synthesis, 1997, 949) (750 mg, 3,8 mmol) e isotiocianato de 4-yodofenilo (1,0 g,

3,8 mmol) por el método del Ejemplo 1. Se obtuvo el compuesto del título como un sólido blanquecino (800 mg, 50%). δ_H (DMSO- d_6) 10,34 (1H, br s), 8,33-8,30 (2H, m), 7,79 (2H, dt, J 2,0, 6,7 Hz), 7,43-7,31 (3H, m), 4,40 (2H, q, J 7,1 Hz), 1,40 (3H, t, J 7,1 Hz), LCMS (ES⁺) RT 4,31 minutos, 425 (M+H)⁺.

EJEMPLO 18

10 2-[(4-Yodo-2-metilfenil)amino]tieno[2,3-b]piridina-3-carbonitrilo

A una solución agitada del Compuesto Intermedio 8 (429 mg, 3,28 mmol) y (2-cloropiridin-3-il)acetonitrilo (D.H. Bremner et al., Synthesis, 1997, 949) (500 mg, 3,28 mmol) en DMSO (20 ml) se añadió hidruro de sodio (164 mg, 4,1 mmol). Cuando hubo cesado el desprendimiento de gases, la mezcla de reacción se calentó durante 3 horas a 80°C. Pasado este tiempo, la mezcla de reacción se vertió en hielo y se extrajo en DCM (2 x 50 ml). Se secaron los componentes orgánicos (Na₂SO₄) y se evaporaron luego a vacío para dar un residuo pardo. La cromatografía en columna (SiO₂, 5:1 hexano:EtOAc) dio el compuesto del título como un polvo amarillo (198 mg, 15%). δ_H (DMSO- d_6) 10,11 (1H, s), 8,29 (1H, dd, J 1,5, 4,7 Hz), 7,75 (2H, m), 7,63 (1H, dd, J 1,7, 8,1 Hz), 7,39 (1H, dd, J 8,1, 4,8 Hz), 7,19 (1H, d, J 8,3 Hz), 2,24 (3H, s), LCMS (ES⁺) RT 3,68 minutos, 392 (M+H)⁺.

EJEMPLO 19

30 2-[(4-Bromo-2-fluorofenil)amino]tieno[2,3-b]piridina-3-carbonitrilo

4-Bromo-2-fluoro-1-isotiocianatobenceno (250 mg, 1,08 mmol) y (2-cloropiridin-3-il)acetonitrilo (D.H. Bremner et al., Synthesis, 1997, 949) (165 mg, 1,08 mmol) se agitaron en DMSO (20 ml) y se añadió en porciones hidruro de sodio (52 mg, 1,3 mmol). Después que hubo finalizado el desprendimiento de gases, la mezcla de

reacción se calentó durante 4 horas a 80°C. Pasado este tiempo, la mezcla de reacción se añadió a hielo (50 ml) y se formó un precipitado. Se filtró éste y se purificó por HPLC preparativa (pH 10, 2-3 min) para dar el compuesto del título como un polvo blanco ((30 mg, 9%). δ_H (DMSO- d_6) 10,45 (1H, s), 8,31 (1H, d, J 3,9 Hz), 7,75 (2H, m), 7,51-7,38 (3H, m), LCMS (ES⁺) RT 3,49 minutos, 350 (M+H)⁺.

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EJEMPLO 202-[(2-Cloro-4-yodofenil)amino]tieno[2,3-*b*]piridina-3-carbonitrilo

El Compuesto Intermedio 9 (300 mg, 1,01 mmol) y (2-cloropiridin-3-il)acetonitrilo (D.H. Bremner et al., Synthesis, 1997, 949) (165 mg, 1,01 mmol) se agitaron juntos en DMSO (20 ml) y se añadió en porciones hidruro de sodio (48 mg, 1,21 mmol). Después que se hubo completado el desprendimiento de gases, la mezcla de reacción se calentó durante 4 h a 80°C. Pasado este tiempo, la mezcla de reacción se añadió a hielo (50 ml) y se extrajo luego en DCM (2 x 50 ml), que se secó (Na₂SO₄) y se evaporó a vacío para dar un residuo amarillo. Este residuo se sometió a cromatografía en columna (SiO₂, 1:4 EtOAc:hexano) para proporcionar el compuesto del título como un polvo amarillo (118 mg, 28%). δ_H (DMSO- d_6) 10,38 (1H, s), 8,35 (1H, dd, J 1,5, 4,8 Hz), 8,00 (1H, d, J 1,9 Hz), 7,80 (2H, m), 7,42 (1H, dd, J 8,0, 4,8 Hz), 7,35 (1H, d, J 8,3 Hz), LCMS (ES⁺) RT 3,70 minutos, 412 (M+H)⁺.

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EJEMPLO 21(2-Amino-2-metilpropil)amida del ácido 2-[(2-fluoro-4-yodofenil)amino]tieno[2,3-*b*]piridina-3-carboxílico

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Se añadió trimetilaluminio (2,85 ml de una solución 2M en hexano, 5,7 mmol) a una solución de 1,2-diamino-2-metilpropano (498 mg, 5,7 mmol) en tolueno (5 ml). Des-

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pués de 10 minutos se añadió el Ejemplo 1 (500 mg, 1,13 mmol) y la mezcla se calentó a 100°C durante 4 h. Después de enfriar, la mezcla de reacción se extinguió con solución de hidróxido de sodio al 10% (75 ml) y se extrajo con EtOAc (100 ml). La fase orgánica se secó (Na₂SO₄) y se concentró a vacío para dar un sólido. La trituration con hexanos (30 ml) y filtración dieron el compuesto del título como un sólido amarillo (248 mg, 45%). δ_H (DMSO-d₆) 10,72 (1H, m), 8,43 (1H, dd, *J* 1,7, 8,0 Hz), 7,84 (1H, dd, *J* 1,7, 4,7 Hz), 7,80-7,40 (2H, s), 7,46-7,35 (2H, m), 7,21 (1H, m), 7,00 (1H, dd, *J* 4,7, 8,0 Hz), 3,40 (2H, d, *J* 5,7 Hz), 1,25 (6H, s), LCMS (ES⁺) RT 2,23 minutos, 501 (M+H)⁺.

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EJEMPLO 22

[(4R)-2,2-Dimetil-[1,3-]dioxolan-4-ilmetoxil]amida del ácido 2-[(2-fluoro-4-yodofenil)amino]tieno[2,3-b]piridina-3-carboxílico

20 Se añadió hidrocloreuro de 1-(3-dimetilaminopropil)-3-carbodiimida (131 mg, 0,68 mmol) a una solución del Compuesto Intermedio 7 (142 mg, 0,34 mmol), 1-hidroxibenzotriazol (93 mg, 0,68 mmol), N-metilmorfolina (0,10 ml, 0,94 mmol) y (4R)-2,2-dimetil-

25 [1,3-]dioxolan-4-ilmetoxilamina (documento WO 02/006213) (101 mg, 0,68 mmol) en N,N-dimetilformamida (5 ml). La mezcla de reacción se agitó a t.a. durante 20 h, y se vertió luego en EtOAc (25 ml). La solución orgánica se lavó con salmuera saturada (2 x 25 ml), se

30 secó a continuación (Na₂SO₄), se filtró y se concentró a vacío para dar un sólido pardo. El producto bruto se sometió a cromatografía en columna (SiO₂, 2:1 hexanos/EtOAc) para dar el compuesto del título como un polvo amarillo pálido (135 mg, 95%). δ_H (DMSO-d₆) 10,98

35 (1H, s), 8,74 (1H, s), 8,28-8,26 (1H, m), 7,94-7,91 (1H, m), 7,48-7,46 (2H, m), 7,37-7,32 (1H, m), 7,23 (1H, dd, *J* 4,8, 8,2 Hz), 4,46-4,40 (1H, m), 4,17 (1H, dd, *J* 3,8, 11,7 Hz), 4,11-4,01 (2H, m), 3,79 (1H, dd, *J*

7,0, 8,3 Hz), 1,15 (3H, s), 1,10 (3H, s), LCMS RT 3,38 minutos, (ES⁻) 542 (M-H)⁻, (ES⁺) 544 (M+H)⁺.

EJEMPLO 23

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[(2R)-2,3-Dihidroxipropoxil]amida del ácido 2-[(2-fluoro-4-yodofenil)amino]tieno[2,3-b]piridina-3-carboxílico

Una solución del Ejemplo 22 (125 mg, 0,23 mmol) en metanol (5 ml) y THF (5 ml) se trató con HCl acuoso al 10% (5 ml). La mezcla de reacción se agitó durante 3,5 h a t.a., y se diluyó luego con EtOAc (25 ml). La solución orgánica se lavó con salmuera saturada (2 x 25 ml), se secó a continuación (Na₂SO₄), se filtró y se concentró a vacío para dar el compuesto del título como un polvo blanco, que se lavó con EtOAc, a continuación con hexanos, y se secó bajo succión (76 mg, 66%). δ_H (DMSO-d₆) 11,31 (1H, s), 10,33 (1H, s), 8,34-8,33 (1H, m), 8,12-8,09 (1H, m), 7,79-7,76 (1H, m), 7,63-7,60 (1H, m), 7,45-7,40 (2H, m), 4,89-4,88 (1H, m), 4,62-4,59 (1H, m), 3,99-3,97 (1H, m), 3,85-3,80 (2H, m), 3,43 (2H, m), LCMS RT 3,38 minutos, (ES⁻) 502 (M-H)⁻, (ES⁺) 504 (M+H)⁺.

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EJEMPLO 24

Éster terc-butílico del ácido (1-{2-[(2-fluoro-4-yodofenil)amino]tieno[2,3-b]piridina-3-carbonil}piperidin-4-il)carbámico

Se preparó a partir del Compuesto Intermedio 7 (150 mg, 0,36 mmol), 1-hidroxibenzotriazol (98 mg, 0,72 mmol), N-metilmorfolina (0,11 ml, 0,99 mmol), hidrocloreuro de 1-(3-dimetilaminopropil)-3-carbodiimida (139 mg, 0,72 mmol) y 4-(BOC-amino)-piperidina (145 mg, 0,72 mmol) por el método del Ejemplo 22. El compuesto del título se evaporó en éter para dar una espuma incolora dura (111 mg, 51%). δ_H (CDCl₃, contiene rotámeros) 9.17 (0.64H, s), 8.90 (0.36H, s), 8.39-8.37 (1H, m), 7,75-

7,73 (0,36H, m), 7,66-7,63 (0,64H, m), 7,53-7,50 (2H, m), 7,44-7,39 (1H, m), 7,31-7,28 (1H, m), 4,57 (0,36H, m), 4,40 (0,64H, m), 4,20-4,15 (1,28H, m), 4,03-3,98 (0,72H, m), 3,72 (1H, m), 3,16-3,08 (2H, m), 2,05-2,00 (2H, m), 1,47 (3,2H, s), 1,44 (5,8H, s), 1,36-1,28 (2H, m), LCMS RT 3,36 minutos, (ES⁻) 595 (M-H)⁻, (ES⁺) 597 (M+H)⁺.

EJEMPLO 25

Dihidrocloruro de (4-aminopiperidin-1-il)amida del ácido 2-[(2-fluoro-4-yodofenil)amino]tieno[2,3-b]piridina-3-carboxílico

Una solución del Ejemplo 24 (99 mg, 0,17 mmol) en metanol (2 ml) se trató con HCl 4M en 1,4-dioxano (5 ml) y se agitó a t.a. durante 3 h. La mezcla de reacción se concentró a vacío para dar una goma amarilla, que se disolvió en agua (25 ml). La solución acuosa se lavó con éter (2 x 25 ml), y se evaporó luego a vacío. La goma resultante se trituró con éter para dar el compuesto del título como un polvo amarillo (89 mg, 94%). δ_H (DMSO-d₆, contiene rotámetros) 9,24 (0,5H, s), 9,14 (0,5H, s), 8,38-8,37 (1H, m), 8,13 (3H, br s), 7,82-7,75 (1H, m), 7,72-7,66 (1H, m), 7,55-7,47 (1H, m), 7,38 (1H, dd, J 4,7, 8,1 Hz), 7,23-7,10 (1H, m), 4,02 (2H, br m), 3,25 (1H, br m), 3,06-2,98 (1H, m), 2,88-2,81 (1H, m), 1,93-1,89 (2H, m), 1,43 (2H, br m), LCMS RT 2,86 minutos, (ES⁺) 497 (M+H)⁺.

EJEMPLO 26

(2-Hidroxi-1-metiletil)amida del ácido 2-[(2-fluoro-4-yodofenil)amino]tieno[2,3-b]piridina-3-carboxílico

Se preparó a partir del Compuesto Intermedio 7 (150 mg, 0,36 mmol), 1-hidroxibenzotriazol (98 mg, 0,72 mmol), N-metilmorfolina (0,11 ml, 0,99 mmol), hidrocloreuro de 1-(3-dimetilaminopropil)-3-carbodiimida (139 mg, 0,72 mmol) y 2-aminopropanol (0,06 ml, 0,72 mmol), por el

método del Ejemplo 22. El producto bruto se sometió a cromatografía en columna (SiO₂, 1:1 hexanos/EtOAc) para dar el compuesto del título, que se recrystalizó en EtOAc/hexanos para dar un polvo beige (56 mg, 33%). δ_H (DMSO-d₆) 10,45 (1H, s), 8,37-8,36 (1H, m), 8,16-8,13 (1H, m), 7,76-7,71 (2H, m), 7,60-7,57 (1H, m), 7,46-7,36 (2H, m), 4,78 (1H, t, J 5,6 Hz), 4,10-4,03 (1H, m), 3,52-3,35 (2H, m), 1,13 (3H, d, J 6,7 Hz), LCMS RT 3,46 minutos, (ES⁺) 472 (M+H)⁺.

EJEMPLO 27

Éster terc-butílico del ácido 3-[(2-[(2-fluoro-4-yodofenil)amino]tieno[2,3-b]piridina-3-carbonil)-amino)metil]-azetidina-1-carboxílico

Se preparó a partir del Compuesto Intermedio 7 (150 mg, 0,36 mmol), 1-hidroxibenzotriazol (98 mg, 0,72 mmol), N-metilmorfolina (0,11 ml, 0,99 mmol), hidrocloreuro de 1-(3-dimetilaminopropil)-3-carbodiimida (139 mg, 0,72 mmol) y 1-BOC-3-(aminometil)azetidina (135 mg, 0,72 mmol) por el método del Ejemplo 22. El producto bruto se sometió a cromatografía en columna (SiO₂, 3:2 hexanos/EtOAc) para dar el compuesto del título, que se recrystalizó en éter/hexanos para dar un polvo de color crema (116 mg, 55%). δ_H (CDCl₃) 8,37 (1H, dd, J 1,3, 4,7 Hz), 7,84 (1H, dd, J 1,3, 8,2 Hz), 7,56-7,53 (2H, m), 7,46-7,41 (1H, m), 7,32 (1H, dd, J 4,7, 8,2 Hz), 6,08 (1H, m), 4,14-4,09 (2H, m), 3,77-3,73 (4H, m), 2,94-2,92 (1H, m), 1,46 (9H, s), LCMS RT 3,68 minutos, (ES⁻) 581 (M-H)⁻, (ES⁺) 583 (M+H)⁺.

EJEMPLO 28

Éster terc-butílico del ácido (1-{2-[(2-fluoro-4-yodofenil)amino]tieno[2,3-b]piridina-3-carbonil}azetidina-3-ilmetil)carbámico

Se preparó a partir del Compuesto Intermedio 7 (150 mg, 0,36 mmol), 1-hidroxibenzotriazol (98 mg, 0,72 mmol),

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N-metilmorfolina (0,11 ml, 0,99 mmol), hidrocloreuro de 1-(3-dimetilaminopropil)-3-carbodiimida (139 mg, 0,72 mmol) y 3-(BOC-aminometil)-azetidina (135 mg, 0,72 mmol), por el método del Ejemplo 22. El compuesto del título se evaporó en éter para dar una espuma incolora dura (75 mg, 36%). δ_H (CDCl₃) 8,25 (1H, dd, J 1,5, 4,7 Hz), 7,67 (1H, dd, J 1,5, 8,1 Hz), 7,46-7,41 (2H, m), 7,38-7,33 (1H, m), 7,22 (1H, dd, J 4,7, 8,1 Hz), 4,59 (1H, br s), 4,15-4,09 (2H, m), 3,80-3,75 (2H, m), 3,32 (2H, m), 2,78-2,74 (1H, m), 1,35 (9H, s), LCMS RT 3,41 minutos, (ES⁻) 581 (M-H)⁻, (ES⁺) 583 (M+H)⁺.

EJEMPLO 29

15 Éster terc-butílico del ácido 3-({2-[(2-fluoro-4-yodo-fenil)amino]tieno[2,3-b]piridina-3-carbonil}amino(azetidina-1-carboxílico

Se preparó a partir del Compuesto Intermedio 7 (150 mg, 0,36 mmol), 1-hidroxibenzotriazol (98 mg, 0,72 mmol), N-metilmorfolina (0,11 ml, 0,99 mmol), hidrocloreuro de 1-(3-dimetilaminopropil)-3-carbodiimida (139 mg, 0,72 mmol) y 1-BOC-3-aminoazetidina (125 mg, 0,72 mmol), por el método del Ejemplo 22. El compuesto del título se recrystalizó en éter/hexanos para dar un polvo de color crema (116 mg, 57%). δ_H (CDCl₃) 8,38 (1H, dd, J 1,2, 4,7 Hz), 7,90 (1H, dd, J 1,2, 8,1 Hz), 7,56-7,53 (2H, m), 7,45-7,40 (1H, m), 7,35 (1H, dd, J 4,7, 8,1 Hz), 6,19 (1H, d, J 6,9 Hz), 4,89-4,84 (1H, m), 4,44-4,38 (2H, m), 3,93-3,88 (2H, m), 1,48 (9H, s), LCMS RT 3,66 minutos, (ES⁻) 567 (M-H)⁻, (ES) 569 (M+H)⁺.

EJEMPLO 30

35 [3-(Aminometil)azetidín-1-il]-{2-[(2-fluoro-4-yodo-fenil)amino]tieno[2,3-b]piridin-3-il}-metanona

Una solución del Ejemplo 28 (65 mg, 0,11 mmol) en DCM (7 ml) se trató con ácido trifluoroacético (3 ml) y se agitó durante 1 h a t.a. La mezcla de reacción se con-

centró a vacío para dar una goma amarilla, que se disolvió en agua (25 ml) y se basificó a pH 10 con carbonato de sodio. La solución acuosa se extrajo con metanol al 5% en DCM (4 x 25 ml), y los extractos se reunieron, se secaron a continuación (Na₂SO₄), se filtraron y se concentraron a vacío. El producto bruto se sometió a cromatografía en columna (SiO₂, 4:1 DCM/metanol) para dar el compuesto del título como un sólido gomoso que se trituró en éter para dar un polvo de color crema (34 mg, 63%). δ_H (DMSO-d₆) 8,31 (1H, m), 7,93 (1H, m), 7,72 (1H, dd, *J* 1,5, 10,5 Hz), 7,55 (1H, m), 7,37 (1H, dd, *J* 4,6, 8,1 Hz), 7,29-7,24 (1H, m), 4,88 (2H, br s), 4,03-3,97 (2H, m), 3,71-3,67 (2H, m), 2,65 (1H, m), 2,70-2,68 (2H, m), LCMS RT 2,93 minutos, (ES⁻) 481 (M-H)⁻, (ES⁺) 483 (M+H)⁺.

EJEMPLO 31

[(2R)-Pirrolidin-2-ilmetil]amida del ácido 2-[(2-fluoro-4-clorofenil)amino]tieno[2,3-b]piridina-3-carboxílico

Una solución del Compuesto Intermedio 10 (135 mg, 0,23 mmol) en metanol (2 ml) se trató con HCl 4M en 1,4-dioxano (5 ml) y se agitó a t.a. durante 30 minutos. La mezcla de reacción se concentró a vacío para dar una goma amarilla, que se disolvió en agua (25 ml). La solución acuosa se lavó con éter (2 x 25 ml), y se basificó luego a pH 11 con hidróxido de amonio acuoso al 25%. La solución acuosa se extrajo con DCM (2 x 25 ml), y los extractos orgánicos se reunieron, se secaron (Na₂SO₄), se filtraron y se concentraron a vacío. El producto bruto se sometió a cromatografía en columna (SiO₂, 91:8:1 DCM/metanol/hidróxido de amonio acuoso al 25%) para dar el compuesto del título, que se liofilizó durante una noche en acetonitrilo/agua para dar un polvo de color crema (73 mg, 65%). δ_H (DMSO-d₆) 10.63 (1H, s), 9.12 (1H, br s), 8.37 (1H, dd, *J* 1.7, 8.0 Hz), 7.84 (1H, dd, *J* 1.7, 4.7 Hz), 7.47 (1H, dd, *J* 2.0, 10.4

Hz), 7.42-7.38, (1H, m), 7.17-7.11, (1H, m), 7.00 (1H, dd, J 4.7, 8.0 Hz), 3.68-3.61, (1H, m), 3.51-3.49, (2H, m), 3.17-3.12, (2H, m), 2.28-1.62 (4H, m). LCMS RT 2,42 minutos, (ES⁻) 495 (M-H)⁻, (ES⁺) 497 (M+H)⁺.

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EJEMPLO 32

10 [(2S)-Pirrolidin-2-ilmetil]amida del ácido 2-[(2-fluoro-4-yodofenil)amino]tieno[2,3-b]piridina-3-carboxílico

Se preparó a partir del Compuesto Intermedio 11 (139 mg, 0,23 mmol) por el método del Ejemplo 31. Se obtuvo el compuesto del título como un polvo de color crema (81 mg, 70%). δ_H (DMSO-d₆) 10.63 (1H, s), 9.12 (1H, br s), 8.37 (1H, dd, J 1.7, 8.0 Hz), 7.84 (1H, dd, J 1.7, 4.7 Hz), 7.47 (1H, dd, J 2.0, 10.4 Hz), 7.42-7.38 (1H, m), 7.17-7.11 (1H, m), 7.00 (1H, dd, J 4.7, 8.0 Hz), 3.68-3.61 (1H, m), 3.51-3.49 (2H, m), 3.17-3.12 (2H, m), 2.28-1.62 (4H, m). LCMS RT 2.42 minutos, (ES) 495 (M-H), (ES⁺) 497 (M+H)⁺.

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EJEMPLO 33

25 Éster terc-butílico del ácido (3S)-3-({2-[(2-fluoro-4-yodo-fenil)amino]tieno[2,3-b]piridina-3-carbonil}amino)-piperidina-1-carboxílico

Se preparó a partir del Compuesto Intermedio 7 (150 mg, 0,36 mmol), 1-hidroxibenzotriazol (98 mg, 0,72 mmol), N-metilmorfolina (0,11 ml, 0,99 mmol), hidrocloreuro de 1-(3-dimetilaminopropil)-3-carbodiimida (139 mg, 0,72 mmol) y (S)-1-BOC-3-aminopiperidina (145 mg, 0,72 mmol) por el método del Ejemplo 22. Se obtuvo el compuesto del título como un sólido gomoso amarillo (131 mg, 61%). δ_H (CDCl₃) 11.34 (1H, s), 8.36-8.34 (1H, m), 7.90-7.88 (1H, m), 7.55-7.52 (2H, m), 7.45-7.42 (1H, m), 7.32-7.29 (1H, m), 5.32 (1H, br s), 4.31 (1H, m), 3.83-3.78 (2H, m), 3.46-3.42 (1H, m), 3.17 (1H, m), 1.89-1.73 (2H, m), 1.67 (2H, m), 1.47 (9H, s). LCMS RT 4.04 minutos, (ES⁺) 597 (M+H)⁺.

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EJEMPLO 34

5 Éster terc-butílico del ácido (3R)-3-((2-[(2-fluoro-4-
10 yodofenil)amino]tieno[2,3-b]piridina-3-carbonil)amino)-
15 piperidina-1-carboxílico

Se preparó a partir del Compuesto Intermedio 7 (150 mg, 0,86 mmol), 1-hidroxibenzotriazol (98 mg, 0,72 mmol), N-metilmorfolina (0,11 ml, 0,99 mmol), hidrocloreuro de
10 1-(3-dimetilaminopropil)-3-carbodiimida (139 mg, 0,72 mmol) y (R)-1-BOC-3-aminopiperidina (145 mg, 0,72 mmol) por el método del Ejemplo 22. Se obtuvo el compuesto del título como un sólido gomoso de color rosa pálido
15 (136 mg, 63%). δ_H (CDCl₃) 11,34 (1H, s), 8.36-8.34 (1H, m), 7.90-7.88 (1H, m), 7.55-7.52 (2H, m), 7.45-7.42 (1H, m), 7.32-7.29 (1H, m), 5.32 (1H, br s), 4.31 (1H, m), 3.83-3.78 (2H, m), 3.46-3.42 (1H, m), 3.17 (1H, m), 1.89-1.73 (2H, m), 1.67 (2H, m), 1.47 (9H, s). LCMS RT 4.03 minutos, (ES⁺) 597 (M+H)⁺.

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EJEMPLO 35

25 Dihidrocloruro de [(3S)-piperidin-3-il]amida del ácido
25 2-[(2-fluoro-4-yodofenil)amino]tieno[2,3-b]piperidina-
30 3-carboxílico

Una solución del Ejemplo 33 (120 mg, 0,20 mmol) en metanol (2 ml) se trató con HCl 4M en 1,4-dioxano (5 ml) y se agitó a t.a. durante 3 h. La mezcla de reacción se
30 evaporó a vacío para dar el compuesto del título como un sólido gomoso amarillo, que se trituroó en éter para dar un polvo amarillo (112 mg, 98%). δ_H (DMSO-d₆) 10.38 (1H, s), 9.04-8.92 (2H, m), 8.38 (1H, dd, J 1.3, 4.6 Hz), 8.17-8.14 (2H, m), 7.75 (1H, dd, J 1.8, 10.4 Hz),
35 7.61-7.58 (1H, m), 7.44 (1H, dd, J 4.6, 8.2 Hz), 7.42-7.36 (1H, m), 4.09 (1H, m), 3.34-3.31 (1H, m), 3.21-3.17 (1H, m), 2.94-2.79 (2H, m), 1.91 (2H, m), 1.74-1.61 (2H, m). LCMS RT 2.38 minutos, (ES⁺) 497 (M+H)⁺.

EJEMPLO 36

5 Dihidrocloruro de [(3R)-piperidin-3-il]amida del ácido
2-[(2-fluoro-4-yodofenil)amino]tieno[2,3-b]piridina-3-
carboxílico

Se preparó a partir del Ejemplo 34 (126 mg, 0,21 mmol)
por el método del Ejemplo 35. El compuesto del título
se obtuvo como un polvo amarillo (115 mg, 96%). δ_H
10 (DMSO- d_6) 0.38 (1H, s), 9.04-8.92 (2H, m), 8.38 (1H, dd,
 J 1.3, 4.6 Hz), 8.17-8.14 (2H, m), 7.75 (1H, dd, J 1.8,
10.4 Hz), 7.61-7.58 (1H, m), 7.44 (1H, dd, J 4.6, 8.2
Hz), 7.42-7.36 (1H, m), 4.09 (1H, m), 3.34-3.31 (1H,
m), 3.21-3.17 (1H, m), 2.94-2.79 (2H, m), 1.91 (2H, m),
15 1.74-1.61 (2H, m). LCMS RT 2.38 minutos, (ES⁺) 497
(M+H)⁺.

EJEMPLO 37

20 Éster terc-butílico del ácido (1-{2-[(2-fluoro-4-
yodofenil)amino]tieno[2,3-b]piridina-3-carbonil})-(3R)-
pirrolidin-3-il)carbámico

Se preparó a partir del Compuesto Intermedio 7 (150 mg,
0,36 mmol), 1-hidroxibenzotriazol (98 mg, 0,72 mmol),
25 N-metilmorfolina (0,11 ml, 0,99 mmol), hidrocloreuro de
1-(3-dimetilaminopropil)-3-carbodiimida (139 mg, 0,72
mmol) y (R)-3-(BOC-amino)-pirrolidina (186 mg, 0,72
mmol), por el método del Ejemplo 22. El producto bruto
se sometió a cromatografía en columna (SiO₂, 3:2 hexa-
30 nos:EtOAc) para dar el compuesto del título, que se e-
vaporó en éter para dar una espuma incolora dura (110
mg, 52%). δ_H (CDCl₃) 9.03 (1H, s), 8.28 (1H, dd, J 1.5,
4.7 Hz), 7.56 (1H, dd, J 1.5, 8.1 Hz), 7.43-7.39 (2H,
m), 7.34-7.29 (1H, m), 7.22-7.18 (1H, m), 4.50 (1H, br
35 s), 4.16-4.14 (1H, m), 3.71 (1H, dd, J 6.2, 11.8 Hz),
3.63-3.56 (2H, m), 3.30 (1H, dd, J 5.1, 11.8 Hz),
2.19-2.12 (1H, m), 1.86-1.77 (1H, m), 1.35 (9H, s).
LCMS RT 3.33 minutos, (ES⁻) 581 (M-H⁺), (ES⁺) 583 (M+H)⁺.

EJEMPLO 38

5 Éster terc-butílico del ácido (1-{2-[(2-fluoro-4-
yodofenil)amino]tieno[2,3-b]piridina-3-carbonil-(3S)-
pirrolidin-3-il)carbámico

Se preparó a partir del Compuesto Intermedio 7 (150 mg, 0,36 mmol), 1-hidroxibenzotriazol (98 mg, 0,72 mmol), N-metilmorfolina (0,11 ml, 0,99 mmol), hidrocloreuro de
10 1-(3-dimetilaminopropil)-3-carbodiimida (139 mg, 0,72 mmol) y (S)-3-(BOC-amino)-pirrolidina (186 mg, 0,72 mmol), por el método del Ejemplo 37. Se obtuvo el compuesto del título como una espuma incolora dura (125 mg, 59%). δ_H (CDCl₃) 9.03 (1H, s), 8.28 (1H, dd, J 1.5, 4.7 Hz), 7.56 (1H, dd, J 1.5, 8.1 Hz), 7.43-7.39 (2H, m), 7.34-7.29 (1H, m), 7.22-7.18 (1H, m), 4.50 (1H, br s), 4.16-4.14 (1H, m), 3.71 (1H, dd, J 6.2, 11.8 Hz), 3.63-3.56 (2H, m), 3.30 (1H, dd, J 5.1, 11.8 Hz), 2.19-2.12 (1H, m), 1.86-1.77 (1H, m), 1.35 (9H, s). LCMS RT
20 3.33 minutos, (ES⁻) 581 (M-H)⁻, (ES⁺) 583 (M+H)⁺.

EJEMPLO 39

25 Éster terc-butílico del ácido (1-{2-[(2-fluoro-4-
yodofenil)amino]tieno[2,3-b]piridina-3-carbonil}azeti-
din-3-il)-carbámico

Se preparó a partir del Compuesto Intermedio 7 (150 mg, 0,36 mmol), 1-hidroxibenzotriazol (98 mg, 0,72 mmol), N-metilmorfolina (0,11 ml, 0,99 mmol), hidrocloreuro de
30 1-(3-dimetilaminopropil)-3-carbodiimida (139 mg, 0,72 mmol) y 3-(BOC-amino)azetidina (125 mg, 0,72 mmol), por el método del Ejemplo 22. El producto bruto se sometió a cromatografía en columna (SiO₂, 3:1 hexanos/EtOAc) para dar el compuesto del título, que se evaporó en éter
35 para dar un polvo de color crema (100 mg, 49%). δ_H (CDCl₃) 10.11 (1H, s), 8.35 (1H, dd, J 1.5, 4.7 Hz), 7.76 (1H, dd, J 1.5, 8.1 Hz), 7.55-7.51 (2H, m), 7.47-7.41 (1H, m), 7.31 (1H, dd, J 4.7, 8.1 Hz), 4.95 (1H,

br s), 4.52 (1H, br s), 4.46-4.40 (2H, m), 4.01-3.96 (2H, m), 1.45 (9H, s). LCMS RT 3.47 minutos, (ES⁻) 567 (M-H)⁻, (ES⁺) 569 (M+H)⁺.

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EJEMPLO 40

Éster terc-butílico del ácido 4-((2-[(2-fluoro-4-yodo-enil)amino]tieno[2,3-b]piridina-3-carbonil)amino)piperidina-1-carboxílico

10 Se preparó a partir del Compuesto Intermedio 7 (150 mg, 0,36 mmol), 1-hidroxibenzotriazol (98 mg, 0,72 mmol), N-metilmorfolina (0,11 ml, 0,99 mmol), hidrocloruro de 1-(3-dimetilaminopropil)-3-carbodiimida (139 mg, 0,72 mmol) y 4-amino-1-BOC-piperidina (145 mg, 0,72 mmol)
15 por el método del Ejemplo 22. El producto bruto se adsorbió sobre SiO₂ y se sometió a cromatografía en columna (SiO₂, 2:1 hexanos/EtOAc) para dar el compuesto del título, que se evaporó en éter para dar escamas de color crema (97 mg, 45%). δ_H (CDCl₃) 11.18 (1H, s), 8.36 (1H, dd, J 1.4, 4.7 Hz), 7.81 (1H, dd, J 1.4, 8.2 Hz), 7.55-7.53 (2H, m), 7.46-7.41 (1H, m), 7.32 (1H, dd, J 4.7, 8.2 Hz), 5.74 (1H, d, J 7.6 Hz), 4.27-4.20 (1H, m), 4.15-4.11 (2H, m), 3.03-2.96 (2H, m), 2.15-2.10 (2H, m), 1.50 (9H, s), 1.45 (2H, m). LCMS RT 3.95 minutos, (ES⁻) 567 (M-H), (ES⁺) 569 (M+H)⁺.
25

EJEMPLO 41

30 [(3R)-3-Aminopirrolidin-1-il]-{2-[(2-fluoro-4-yodo-fenil)mino]tieno[2,3-b]piridin-3-il}-metanona
Preparada a partir del Ejemplo 37 (100 mg, 0,17 mmol) siguiendo el método del ejemplo 35. Se obtuvo el compuesto del título como un polvo amarillo (100 mg, quant.). δ_H (DMSO-d₆) 9.29 (1H, s), 8.36 (1H, dd, J 1.5, 4.7 Hz), 8.29 (3H, s), 7.91-7.89 (1H, m), 7.72 (1H, dd, J 1.8, 10.4 Hz), 7.55-7.52 (1H, m), 7.37 (1H, dd, J 4.7, 8.1 Hz), 7.24-7.19 (1H, m), 3.79-3.72 (1H, m), 3.70-3.58 (2H, m), 3.51-3.38 (2H, m), 2.20-2.13 (1H, m),
35

m), 2.01-1.97 (1H, m). LCMS RT 2.24 minutos, (ES⁻) 481 (M-H⁻), (ES⁺) 483 (M+H)⁺.

EJEMPLO 42

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[(3S)-3-Aminopirrolidin-1-il]-{2-[(2-fluoro-4-yodo-
fenil)amino]tieno[2,3-b]piridin-3-il}metanona

Se preparó a partir del Ejemplo 38 (115 mg, 0,20 mmol) siguiendo el método del Ejemplo 35. Se obtuvo el compuesto del título como un polvo amarillo (109 mg, 99%).
10 δ_H (DMSO-d₆) 9.29 (1H, s), 8.36 (1H, dd, J 1.5, 4.7 Hz), 8.29 (3H, s), 7.91-7.89 (1H, m), 7.72 (1H, dd, J 1.8, 10.4 Hz), 7.55-7.52 (1H, m), 7.37 (1H, dd, J 4.7, 8.1 Hz), 7.24-7.19 (1H, m), 3.79-3.72 (1H, m), 3.70-3.58
15 (2H, m), 3.51-3.38 (2H, m), 2.20-2.13 (1H, m), 2.01-1.97 (1H, m). LCMS RT 2.24 minutos, (ES⁻) 481 (M-H)⁻, (ES⁺) 483 (M+H)⁺.

EJEMPLO 43

20

(Piperidin-4-il)amida del ácido 2-[(2-fluoro-4-
yodofenil)-amino]tieno[2,3-b]piridina-3-carboxílico

Preparada a partir del Ejemplo 40 (87 mg, 0,15 mmol) siguiendo el método del Ejemplo 35. Se obtuvo el compuesto del título como un polvo amarillo (80 mg, 96%). δ_H
25 (DMSO-d₆) 10.31 (1H, s), 8.84 (1H, m), 8.68 (1H, m), 8.38 (1H, dd, J 1.3, 4.6 Hz), 8.24 (1H, d, J 7.5 Hz), 8.09 (1H, dd, J 1.3, 8.2 Hz), 7.74 (1H, dd, J 1.8, 10.5 Hz), 7.59-7.57 (1H, m), 7.44 (1H, dd, J 4.7, 8.2 Hz),
30 7.39-7.34 (1H, m), 4.05-3.97 (1H, m), 3.32-3.27 (2H, m), 3.03-2.87 (2H, m), 2.00-1.97 (2H, m), 1.82-1.71 (2H, m). LCMS RT 2.40 minutos, (ES⁻) 495 (M-H)⁻, (ES⁺) 497 (M+H)⁺.

35

EJEMPLO 44

3-Aminoazetidin-1-il)-{2-[(2-fluoro-4-yodofenil)amino]-
tieno[2,3-b]piridin-3-il}-metanona

Preparada a partir del Ejemplo 39 (90 mg, 0,16 mmol) por el método del Ejemplo 30. La mezcla de reacción se concentró a vacío para dar una goma amarilla, que se disolvió en metanol (5 ml) y agua (5 ml) y se basificó a pH 10 con hidróxido de amonio aq. al 25%. La solución acuosa se concentró a vacío sobre SiO₂, y el producto bruto se sometió a cromatografía en columna (SiO₂, 95:4:1 DCM/metanol/hidróxido de amonio aq. al 25%). El compuesto del título se liofilizó durante una noche en acetonitrilo/metanol/agua para dar un polvo de color crema (31 mg) 42%). δ_H (DMSO-d₆) 8.33 (1H, dd, *J* 1.5, 4.7 Hz), 7.94 (1H, dd, *J* 1.5, 8.1 Hz), 7.73 (1H, dd, *J* 1.9, 10.5 Hz), 7.54 (1H, ddd, *J* 0.9, 0.9, 8.4 Hz), 7.38 (1H, dd, *J* 4.7, 8.1 Hz), 7.31-7.26 (1H, m), 4.23-4.11 (2H, m), 3.72-3.59 (3H, m). LCMS RT 3.00 minutos, (ES⁻) 467 (m-H)⁻, (ES⁺) 469 (M+H)⁺.

EJEMPLO 45

Bis(2-hidroxietil)amida del ácido 2-[(2-fluoro-4-yodo-fenil)amino]tieno[2,3-b]piridina-3-carboxílico

Preparada a partir del Compuesto Intermedio 7 (150 mg, 136 mmol), 1-hidroxibenzotriazol (98 mg, 0,72 mmol), N-metilmorfolina (0,11 ml, 0,99 mmol), hidrocloreuro de 1-(3-dimetilaminopropil)-3-carbodiimida (139 mg, 0,72 mmol) y dietanolamina (76 mg, 0,72 mmol) por el método del Ejemplo 22. El producto bruto se sometió a cromatografía en columna (SiO₂, EtOAc, 2 veces) para dar el compuesto del título, que se liofilizó durante una noche en acetonitrilo/agua para dar un polvo de color crema (62 mg, 34%) δ_H (DMSO-d₆) 8.79 (1H, br s), 8.38 (1H, dd, *J* 1.5, 4.7 Hz), 7.77 (1H, dd, *J* 1.5, 8.1 Hz), 7.67 (1H, dd, *J* 1.9, 10.5 Hz), 7.69-7.46 (1H, m), 7.38 (1H, dd, *J* 4.7, 8.1 Hz), 7.18-7.12 (1H, m), 4.83 (2H, br s), 3.30 (8H, s). LCMS RT 3.01 minutos, (ES⁺) 502 (M+H)⁺.

EJEMPLO 46

{2-[(2-Fluoro-4-yodofenil)amino]tieno[2,3-b]piridin-3-il)-(3-hidroxiazetidín-1-il)-metanona

Preparada a partir del Compuesto Intermedio 7 (225 mg, 0,54 mmol), 1-hidroxibenzotriazol (147 mg, 1,08 mmol), N-metilmorfolina (0,16 ml, 1,48 mmol), hidrocloreuro de 1-(3-dimetilaminopropil)-3-carbodiimida (208 mg, 1,08 mmol) e hidrocloreuro de 3-hidroxiazetidina (120 mg, 1,08 mmol) por el método del Ejemplo 22. Después de cromatografía, se recristalizó el compuesto del título en metanol/éter para dar un polvo blanco (125 mg, 49%).

²⁹ (DMSO-d₆) 9.60 (1H, s), 8.35-8.34 (1H, m), 7.94 (1H, dd, J 1.4, 8.1 Hz), 7.75-7.71 (1H, m), 7.57-7.54 (1H, m), 7.41-7.37 (1H, m), 7.31-7.25 (1H, m), 5.68 (1H, d, J 6.0 Hz), 4.47-4.44 (1H, m), 4.21-4.16 (2H, m), 3.79-3.74 (2H, m). LCMS RT 3.31 minutos, (ES⁺) 470 (M+H)⁺.

EJEMPLO 47

{2-[(2-Fluoro-4-yodofenil)amino]tieno[2,3-b]piridin-3-il)-[(3R)-3-hidroxipirrolidín-1-il]-metanona

Preparada a partir del Compuesto Intermedio 7 (150 mg, 0,36 mmol), 1-hidroxibenzotriazol (98 mg, 0,72 mmol), N-metilmorfolina (0,11 ml, 0,99 mmol), hidrocloreuro de 1-(3-dimetilaminopropil)-3-carbodiimida (139 mg, 0,72 mmol) y (R)-3-hidroxipirrolidina (63 mg, 0,72 mmol) por el método del Ejemplo 22. Después de cromatografía, se liolifizó el compuesto del título durante una noche en acetonitrilo/agua para dar un polvo de color crema (116 mg, 66%).

^{δ_H} (DMSO-d₆) 9.20 (1H, s), 8.35 (1H, dd, J 1.5, 4.7 Hz), 7.81 (1H, dd, J 1.5, 8.1 Hz), 7.67 (1H, dd, J 1.9, 10.5 Hz), 7.50-7.47 (1H, m), 7.36 (1H, dd, J 4.7, 8.1 Hz), 7.17-7.11 (1H, m), 4.91 (1H, s), 4.22 (1H, s), 3.54-3.30 (3H, m), 3.21-3.17 (1H, m), 1.90-1.74 (2H, m). LCMS RT 3.18 minutos, (ES⁺) 484 (M+H)⁺.

EJEMPLO 48

{2-[(2-Fluoro-4-yodofenil)amino]tieno[2,3-b]piridin-3-il)}-[(3S)-3-hidroxi-pirrolidin-1-il]-metanona

Preparada a partir del Compuesto Intermedio 7 (150 mg, 0,36 mmol), 1-hidroxibenzotriazol (98 mg, 0,72 mmol),
5 N-metilmorfolina (0,11 ml, 0,99 mmol), hidrocloreuro de 1-(3-dimetilaminopropil)-3-carbodiimida (139 mg, 0,72 mmol) y (S)-3-hidroxi-pirrolidina (63 mg, 0,72 mmol, por el método del Ejemplo 47. El compuesto del título se obtuvo como un polvo de color crema (105 mg, 60%). δ_H
10 (DMSO- d_6) 9.20 (1H, s), 8.35 (1H, dd, J 1.5, 4.7 Hz), 7.81 (1H, dd, J 1.5, 8.1 Hz), 7.67 (1H, dd, J 1.9, 10.5 Hz), 7.50-7.47 (1H, m), 7.36 (1H, dd, J 4.7, 8.1 Hz), 7.17-7.11 (1H, m), 4.91 (1H, s), 4.22 (1H, s), 3.54-3.30 (3H, m), 3.21-3.17 (1H, m), 1.90-1.74 (2H, m).
15 LCMS RT 3.17 minutos, (ES⁺) 484 (M+H)⁺.

EJEMPLO 49

{2-[(2-Fluoro-4-yodofenil)amino]tieno[2,3-b]piridin-3-il)}-[2-(hidroximetil)-piperidin-1-il]-metanona

Preparada a partir del Compuesto Intermedio 7 (150 mg, 0,36 mmol), 1-hidroxibenzotriazol (98 mg, 0,72 mmol),
N-metilmorfolina (0,11 ml, 0,99 mmol), hidrocloreuro de 1-(3-dimetilaminopropil)-3-carbodiimida (139 mg, 0,72
25 mmol) y 2-piperidinametanol (83 mg, 0,72 mmol), por el método del Ejemplo 22. Después de cromatografía, se recristalizó el compuesto del título en EtOAc/hexanos para dar un polvo amarillo pálido (44 mg, 24%). δ_H (DMSO- d_6 , 130°C) 8.38 (1H, dd, J 1.5, 4.7 Hz), 7.83 (1H, dd, J
30 1.5, 8.0 Hz), 7.59 (1H, dd, J 1.9, 10.5 Hz), 7.47 (1H, d, J 8.5 Hz), 7.35 (1H, dd, J 4.7, 8.0 Hz), 7.16 (1H, dd, J 8.8, 8.8 Hz), 4.30 (1H, br s), 4.21 (1H, m), 3.89 (1H, m), 3.65-3.60 (1H, m), 3.51-3.47 (1H, m), 3.03-2.97 (1H, m), 1.74-1.72 (1H, m), 1.65-1.56 (4H, m),
35 1.37 (1H, m). LCMS RT 2.86 minutos, (ES⁻) 510 (M-H)⁻, (ES⁺) 512 (M+H)⁺.

EJEMPLO 50

{2-[(2-Fluoro-4-yodofenil)amino]tieno[2,3-b]piridin-3-il)-(3S)-3-(hidroximetil)morfolin-4-il}-metanona

Preparada a partir del Compuesto Intermedio 7 (150 mg, 0,36 mmol), 1-hidroxibenzotriazol (98 mg, 0,72 mmol), N-metilmorfolina (0,11 ml, 0,99 mmol), hidrocloreto de 1-(3-dimetilaminopropil)-3-carbodiimida (139 mg, 0,72 mmol) y (3S)-3-(hidroximetil)morfolina (85 mg, 0,72 mmol), por el método del Ejemplo 22. Después de cromatografía, el compuesto del título se liofilizó durante una noche en acetónitrilo/agua para dar un polvo de color crema (81 mg, 44%). δ_H (DMSO- d_6 , 120°C) 8.37-8.36 (1H, m), 7.85-7.83 (1H, m), 7.60 (1H, dd, J 1.8, 10.5 Hz), 7.49-7.47 (1H, m), 7.35 (1H, dd, J 4.7, 8.0 Hz), 7.15 (1H, dd, J 8.7, 8.7 Hz), 3.99 (1H, m), 3.85 (1H, d, J 11.6 Hz), 3.80-3.77 (1H, m), 3.70-3.67 (1H, m), 3.65-3.56 (2H, m), 3.48-3.45 (1H, m), 3.34 (1H, m), 3.27-3.21 (1H, m). LCMS RT 2.60 minutos, (ES⁻) 512 (M-H)⁻, (ES⁺) 514 (M+H)⁺.

EJEMPLO 51

Éster terc-butílico del ácido 4-{2-[(2-fluoro-4-yodofenil)amino]tieno[2,3-b]piridina-3-carbonil}-(3R)-3-(hidroximetil)piperazina-1-carboxílico

Preparada a partir del Compuesto Intermedio 7 (150 mg, 0,36 mmol), 1-hidroxibenzotriazol (98 mg, 0,72 mmol), N-metilmorfolina (0,11 ml, 0,99 mmol), hidrocloreto de 1-(3-dimetilaminopropil)-3-carbodiimida (139 mg, 0,72 mmol) y (2R)-4-BOC-2-(hidroximetil)piperazina (157 mg, 0,72 mmol), por el método del Ejemplo 22. El producto bruto se sometió a cromatografía en columna (SiO₂, 1:1 hexanos/EtOAc) para dar el compuesto del título, que se evaporó en éter para dar una espuma dura de color rosa pálido (95 mg, 43%). δ_H (DMSO- d_6 , 120°C) 8.53 (1H, br s), 8.38-8.37 (1H, m), 7.86-7.84 (1H, m), 7.60 (1H, dd, J 1.7, 10.5 Hz), 7.49 (1H, d, J 8.5 Hz), 7.36 (1H, dd, J 4.7, 8.0 Hz), 7.19-7.15 (1H, dd, J 8.5, 8.7 Hz),

4.52 (1H, br s), 4.16 (1H, m), 3.95 (1H, d, J 13.5 Hz), 3.88-3.81 (2H, m), 3.49-3.43 (2H, m), 3.14-3.10 (1H, m), 3.02-2.95 (1H, m), 1.43 (9H, s). LCMS RT 2.98 minutos, (ES⁺) 613 (M+H)⁺.

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EJEMPLO 522-[(2-Fluoro-4-yodofenil)amino]tieno[2,3-*b*]piridina-7-óxido

- 10 Se suspendió el Ejemplo 8 (250 mg, 0,55 mmol) en una mezcla de etanol (20 ml) y agua (10 ml). Se añadió hidróxido de litio hidratado (24,0 mg, 0,57 mmol) y la mezcla se calentó a reflujo durante 24 horas. Después de concentración y liofilización, la mezcla se purificó
- 15 por cromatografía (sílice, diclorometano y luego MeOH al 2% en diclorometano). Se obtuvo el compuesto del título como un sólido blanquecino (50 mg, 24%). δ_H (DMSO- d_6) 9.42 (1H, br s), 8.13 (1H, dd, J 0.7, 6.2 Hz), 7.69 (1H, dd, J 1.9, 10.7 Hz), 7.54-7.51 (2H, m), 7.39-7.32
- 20 (2H, m), 6.73 (1H, s). LCMS (ES⁺) RT 2.84 minutos, 387 (M+H)⁺.

EJEMPLO 532-[(2-Fluoro-4-yodofenil)amino]-N-[2-(morfolin-4-il)-etil]tieno[2,3-*b*]piridina-3-carboxamida

- Preparada a partir del Ejemplo 1 (250 mg, 0,56 mmol) y 4-(2-aminoetil)morfolina (292 mg, 2,24 mmol) por el método del Ejemplo 5. Después de cromatografía (5% metanol, 95% diclorometano) se obtuvo el compuesto del título como un sólido blanquecino (140 mg, 47%). δ_H (CDCl₃) 11.43 (1H, br s), 8.36 (1H, dd, J 1.4, 4.7 Hz), 8.03 (1H, dd, J 1.4, 8.2 Hz), 7.55-7.51 (2H, m), 7.44 (1H, dd, J 8.2, 8.2 Hz), 7.32 (1H, dd, J 4.7, 8.2 Hz),
- 30 6.84 (1H, br s), 3.80-3.77 (4H, m), 3.67-3.62 (2H, m), 2.73-2.69 (2H, m), 2.62-2.59 (4H, m). LCMS (ES⁺) RT 2.37 minutos, 527 (M+H)⁺.

EJEMPLO 54

2-[4-((2-[(2-Fluoro-4-yodofenil)amino]tieno[2,3-b]piridin-3-il)carbonil)piperazin-1-il]etanol

- 5 Se preparó a partir del Ejemplo 1 (250 mg, 0,56 mmol) y N-(2-hidroxietil)piperazina (292 mg, 2,24 mmol) por el método del Ejemplo 5. Después de cromatografía (5% metanol, 95% diclorometano) se obtuvo el compuesto del título como un sólido blanco (86 mg, 29%). δ_H (DMSO- d_6)
- 10 9.13 (1H, br s), 8.36 (1H, dd, J 1.5, 4.7 Hz), 7.80 (1H, dd, J 1.5, 8.1 Hz), 7.68 (1H, dd, J 1.9, 10.5 Hz), 7.49-7.45 (1H, m), 7.37 (1H, dd, J 4.7, 8.1 Hz), 7.10 (1H, dd, J 8.7, 8.7 Hz), 4.37 (1H, t, J 5.4 Hz), 3.50-3.40 (6H, m), 2.37-2.33 (6H, m). LCMS (ES^+) RT 2.16 minutos,
- 15 527 (M+H) $^+$.

EJEMPLO 55

3-(1,4-Diazepan-1-ilcarbonil)-N-(2-fluoro-4-yodofenil)-tieno[2,3-b]piridin-2-amina

- 20 Preparada a partir del Ejemplo 1 (250 mg, 0,56 mmol) y homopiperazina (224 mg, 2,24 mmol) por el método del Ejemplo 5. Después de cromatografía (metanol al 10-15% en diclorometano) se obtuvo el compuesto del título como un sólido amarillo pálido (180 mg, 64%). δ_H (CDCl $_3$)
- 25 8.99 (1H, br s), 8.34 (1H, dd, J 1.6, 4.7 Hz), 7.74 (1H, dd, J 1.6, 8.1 Hz), 7.47-7.43 (2H, m), 7.35 (1H, dd, J 8.5, 8.5 Hz), 7.28-7.22 (1H, m), 4.30-4.10 (1H, br m), 3.95-3.80 (1H, br m), 3.39-2.86 (6H, br m),
- 30 2.17-1.77 (3H, br m). LCMS (ES^+) RT 2.17 minutos, 497 (M+H) $^+$.

EJEMPLO 56

N-[3-(Dimetilamino)-2,2-dimetilpropil]-2-[(2-fluoro-4-yodofenil)amino]tieno[2,3-b]piridina-3-carboxamida

Preparada a partir del Ejemplo 1 (250 mg, 0,56 mmol) y N,N,2,2-tetrametil-1,3-propanodiamina (292 mg, 2,24

mmol) por el método del Ejemplo 5. Después de cromatografía (5% metanol, 95% diclorometano) se obtuvo el compuesto del título como un sólido amarillo pálido (60 mg, 20%). δ_H (DMSO- d_6) 10.81 (1H, br s), 9.10 (1H, br s), 8.24-8.21 (2H, m), 7.69-7.65 (1H, m), 7.55-7.52 (1H, m), 7.37-7.31 (2H, m), 3.29-3.27 (2H, m), 2.50-2.37 (8H, br m), 0.96 (6H, s). LCMS (ES⁺) RT 2.39 minutos, 527 (M+H)⁺.

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EJEMPLO 57

2-[(2-Fluoro-4-yodofenil)amino]-N-[3-(morfolin-4-il)-propil]tieno[2,3-b]piridina-3-carboxamida

Preparada a partir del Ejemplo 1 (250 mg, 0,56 mmol) y 4-(3-aminopropil)morfolina (323 mg, 2,24 mmol) por el método del Ejemplo 5. Después de cromatografía (5% metanol, 95% diclorometano) se obtuvo el compuesto del título como un sólido amarillo pálido (115 mg, 38%). δ_H (CDCl₃) 11.29 (1H, br s), 8.36 (1H, dd, *J* 1.4, 4.7 Hz), 7.99 (1H, dd, *J* 1.4, 8.2 Hz), 7.63-7.51 (2H, m), 7.47-7.41 (1H, m), 7.33-7.29 (1H, m), 7.12 (1H, br s), 3.70-3.64 (2H, m), 3.60-3.56 (4H, m), 2.58-2.54 (2H, m), 2.49-2.46 (4H, m), 1.90-1.82 (2H, m). LCMS (ES⁺) RT 2.34 minutos, 541 (M+H)⁺.

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EJEMPLO 58

N-(2-Fluoro-4-yodofenil)-3-(piperazin-1-ilcarbonil)-tieno[2,3-b]piridin-2-amina

Se disolvió piperazina (3,90 g, 45,2 mmol) en tolueno seco (100 ml) bajo nitrógeno. La mezcla se puso en un baño de agua a 20°C y se añadió lentamente trimetilaluminio (2,0M en tolueno, 22,6 ml, 45,2 mmol). Después de 10 minutos, se añadió el Ejemplo 1 (4,00 g, 0,56 mmol). La mezcla se calentó a 100°C bajo nitrógeno durante 6 horas. Después de enfriar a la temperatura ambiente, se vertió la mezcla sobre una suspensión espesa de sílice (100 g) en cloroformo (400 ml) y metanol (200 ml). Des-

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pués de agitar durante 10 minutos, se dejó la mezcla en reposo durante una noche. La filtración, y concentración del disolvente orgánico a vacío, dieron un material bruto, que se purificó por trituración con dietil-éter (50 ml), filtración y lavado con dietil-éter (20 ml). El compuesto del título se aisló como un sólido amarillo (3,56 g, 82%), que podía utilizarse para procesos químicos posteriores. La sal dihidrocloruro del compuesto del título se preparó por disolución de la base libre (1,60 g, 3,32 mmol) en diclorometano (30 ml) y metanol (5 ml). Se añadió HCl en éter (2,0M, 3,34 ml, 6,70 mmol) y la mezcla se concentró a vacío. La trituración con dietil-éter (40 ml) y filtración dio la sal dihidrocloruro del compuesto del título (1.80 g, 98%).

15 δ_H (DMSO- d_6) 9.75 (0.25H, br s), 9.43 (1.75H, br s), 9.30 (1H, s), 8.36 (1H, dd, J 1.6, 4.7 Hz), 7.87 (1H, dd, J 1.6, 8.1 Hz), 7.72 (1H, dd, J 1.9, 10.6 Hz), 7.53 (1H, m), 7.39 (1H, dd, J 4.7, 8.1 Hz), 7.22 (1H, dd, J 8.5, 8.5 Hz), 3.75-3.58 (4H, m), 3.17-3.06 (4H, m). LCMS

20 (ES^+) RT 2.19 minutos, 483 ($M+H$) $^+$.

EJEMPLO 59

[4-({2-[(2-Fluoro-4-yodofenil)amino]tieno[2,3-b]piridin-3-il}carbonil)-piperazin-1-il]acetato de etilo

Se disolvió el Ejemplo 58 (300 mg, 0,62 mmol) en diclorometano (10 ml) y se añadieron trietilamina (94 μ l, 0,65 mmol) y cloroacetato de etilo (56 μ l, 0,65 mmol). La mezcla se calentó a reflujo durante 12 horas. Después de enfriar y repartir entre diclorometano y agua (25 ml de cada uno), se secó la capa orgánica (Na_2SO_4) y se concentró a vacío. La purificación por cromatografía (sílice, 3% metanol, 97% diclorometano) dio el producto como un aceite, que se disolvió en dietil-éter (5 ml) y se concentró a alto vacío para dar el compuesto del título como un sólido blanco (240 mg, 68%). δ_H ($CDCl_3$) 9.11 (1H, br s), 8.37 (1H, dd, J 1.5, 4.7 Hz), 7.71

(1H, dd, J 1.5, 8.1 Hz), 7.53-7.49 (214, m), 7.40 (1H, dd, J 8.4, 8.4 Hz), 7.32-7.28 (1H, m), 4.21 (2H, q, J 7.1 Hz), 3.75-3.61 (4H, m), 3.31 (2H, s), 2.79-2.62 (4H, m), 1.29 (3H, t, J 7.1 Hz). LCMS (ES⁺) RT 3.26 minutos, 569 (M+H)⁺.

EJEMPLO 60

Ácido [4-({2-[(2-fluoro-4-yodofenil)amino]tieno[2,3-*b*]-piridin-3-il}carbonil)piperazin-1-il]acético
Se disolvió el Ejemplo 59 (213 mg, 0,375 mmol) en etanol (7 ml) y agua (7 ml). Se añadió hidróxido de sodio (15,0 mg, 0,375 mmol) y la mezcla se agitó a la temperatura ambiente durante 18 horas. La liofilización dio el compuesto del título como su sal de sodio (200 mg, 99%). δ_H (DMSO- d_6) 9.29 (1H, br s), 8.22-8.17 (1H, br m), 7.68 (1H, br d, J 8.0 Hz), 7.56 (1H, br d, J 10.4 Hz), 7.40 (1H, br d, J 8.6 Hz), 7.28-7.20 (1H, br m), 7.07 (1H, dd, J 8.6, 8.6 Hz), 3.42-3.38 (4H, m), 2.65 (2H, s), 2.37-2.35 (4H, m). LCMS (ES⁺) RT 2.64 minutos, 541 (M+H)⁺.

EJEMPLO 61

(3R)-3-[(2-[(2-Fluoro-4-yodofenil)amino]-tieno[2,3-*b*]piridin-3-il}carbonil)amino]pirrolidina-1-carboxilato de terc-butilo
Se preparó a partir del Ejemplo 1 (250 mg, 0,56 mmol) y (R)-3-amino-1-terc-butoxicarbonilpirrolidina (417 mg, 2,24 mmol) por el método del Ejemplo 5. Después de cromatografía (25% acetato de etilo, 75% diclorometano) se obtuvo el compuesto del título como un sólido blanquecino (45 mg, 13%). δ_H (DMSO- d_6) 10.27 (1H, br s), 8.35 (1H, dd, J 1.4, 4.7 Hz), 8.23 (1H, br d, J 6.5 Hz), 8.06 (1H, dd, J 1.4, 8.2 Hz), 7.74 (1H, dd, J 1.9, 10.5 Hz), 7.57 (1H, d, J 8.5 Hz), 7.43 (1H, dd, J 4.7, 8.2 Hz), 7.36 (1H, dd, J 8.6, 8.6 Hz), 4.46-4.40 (1H, br in), 3.57-3.54 (1H, m), 3.52-3.30 (3H, m), 2.15-2.05

(1H, br m), 1.95-1.85 (1H, br m), 1.41 (9H, s). LCMS (ES⁺) RT 3.70 minutos, 583 (M+H)⁺.

EJEMPLO 62

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(3S)-3-[(2-[(2-Fluoro-4-yodofenil)amino]tieno[2,3-b]-piridin-3-il)-carbonil)amino]pirrolidina-1-carboxilato de terc-butilo

Se preparó a partir del Ejemplo 1 (250 mg, 0,56 mmol) y
10 (S)-3-amino-1-terc-butoxicarbonilpirrolidina (417 mg, 2,24 mmol) por el método del Ejemplo 5. Después de cromatografía (25% acetato de etilo, 75% diclorometano) se obtuvo el compuesto del título como un sólido blanquecino (190 mg, 58%). δ_H (DMSO-d₆) 10.27 (1H, br s), 8.35
15 (1H, dd, *J* 1.4, 4.7 Hz), 8.23 (1H, br d, *J* 6.5 Hz), 8.06 (1H, dd, *J* 1.4, 8.2 Hz), 7.74 (1H, dd, *J* 1.9, 10.5 Hz), 7.57 (1H, d, *J* 8.5 Hz), 7.43 (1H, dd, *J* 4.7, 8.2 Hz), 7.36 (1H, dd, *J* 8.6, 8.6 Hz), 4.46-4.40 (1H, br m), 3.57-3.54 (1H, m), 3.52-3.30 (3H, m), 2.15-2.05
20 (1H, br m), 1.95-1.85 (1H, br m), 1.41 (9H, s). LCMS (ES⁺) RT 3.70 minutos, 583 (M+H)⁺.

EJEMPLO 63

25 2-[(2-Fluoro-4-yodofenil)amino]-N-[(3R)-pirrolidin-3-il]tieno[2,3-b]piridina-3-carboxamida

Se disolvió el ejemplo 61 (40 mg, 0,069 mmol) en diclorometano (3 ml) y se añadió HCl en dioxano (4,0M, 1,0 ml, 4,0 mmol). La mezcla se agitó a la temperatura ambiente durante 18 horas. El sólido resultante se separó por filtración y se secó a vacío a 40°C para dar la sal dihidrocloruro del compuesto del título (28 mg, 73%). δ_H (DMSO-d₆) 10.44 (1H, br s), 9.25 (2H, br m), 8.37-8.31 (2H, m), 8.21 (1H, dd, *J* 1.3, 8.2 Hz), 7.76 (1H, dd, *J* 1.8, 10.4 Hz), 7.61 (1H, d, *J* 8.5 Hz), 7.45-7.39 (2H, m), 4.61-4.57 (1H, m), 3.45-3.23 (4H, m), 2.27-2.15 (1H, m), 2.09-1.98 (1H, m). LCMS (ES⁺) RT 2.30 minutos, 483 (M+H)⁺.

EJEMPLO 642-[(2-Fluoro-4-yodofenil)amino]-N-[(3S)-pirrolidin-3-il]tieno[2,3-b]piridina-3-carboxamida

Se disolvió el Ejemplo 62 (170 mg, 0,069 mmol) en diclorometano (4 ml) y se añadió HCl en dioxano (4,0M, 4,0 ml, 16,0 mmol). La mezcla se agitó a la temperatura ambiente durante 18 horas. El sólido resultante se separó por filtración y se secó a vacío a 40°C para dar la sal dihidrocloruro del compuesto del título (150 mg, 92%). δ_H (DMSO- d_6) 10.44 (1H, br s), 9.25 (2H, br m), 8.37-8.31 (2H, m), 8.21 (1H, dd, J 1.3, 8.2 Hz), 7.76 (1H, dd, J 1.8, 10.4 Hz), 7.61 (1H, d, J 8.5 Hz), 7.45-7.39 (2H, m), 4.61-4.57 (1H, m), 3.45-3.23 (4H, m), 2.27-2.15 (1H, m), 2.09-1.98 (1H, m). LCMS (ES⁺) RT 2.30 minutos, 483 (M+H)⁺.

EJEMPLO 652-[(2-Fluoro-4-yodofenil)amino]-N-(1-metilpiperidin-4-il)tieno[2,3-b]piridina-3-carboxamida

Preparada a partir del Ejemplo 1 (250 mg, 0,56 mmol) y 4-amino-1-metilpiperidina (255 mg, 2,24 mmol) por el método del Ejemplo 5. Después de cromatografía (10% metanol, 90% diclorometano) el material bruto se disolvió en diclorometano (2 ml) y se añadió HCl 2,0M en dietiléter (2 ml). El sólido resultante se separó por filtración para dar la sal dihidrocloruro del compuesto del título como un sólido amarillo (145 mg, 44%). δ_H (DMSO- d_6) 10.62 (1H, br s), 10.37 (0.8H, s), 10.26 (0.2H, s), 8.40-8.36 (1H, m), 8.31-8.28 (0.8H, m), 8.22-8.20 (0.2H, m), 8.19-8.16 (0.2H, m), 8.10-8.07 (0.8H, m), 7.75-7.71 (1H, m), 7.59-7.56 (1H, m), 7.47-7.31 (2H, m), 4.05 (1H, br m), 3.45-3.05 (5H, m), 2.70 (3H, d, J 6.0 Hz), 2.03-1.85 (4H, m). LCMS (ES⁺) RT 2.34 minutos, 511 (M+H)⁺.

1,18 mmol) y la mezcla de reacción se agitó durante 1 hora más a la temperatura ambiente. Se vertió la mezcla de reacción sobre agua y se extrajo en acetato de etilo. La fase orgánica se lavó con salmuera, se secó (sulfato de magnesio) y se concentró a vacío. El producto bruto se purificó por cromatografía (SiO₂; metanol al 10% en acetato de etilo), dando el producto requerido como un sólido amarillo pálido (64 mg). δ_H (DMSO-d₆) 9.41 (1H, s), 8.20 (1H, dd, *J* 5.9, 1.0 Hz), 7.74 (1H, dd, *J* 10.3, 1.9 Hz), 7.57-7.54 (1H, m), 7.48-7.38 (2H, m), 7.22 (1H, t, *J* 8.6 Hz), 3.47 (3H, s), 3.17 (3H, s). LCMS (ES⁺) RT 2.70 minutos, 474 (M+H)⁺.

EJEMPLO 69

(N-Metoxi-N-metil)amida del ácido 2-[(2-fluoro-4-yodofenil)amino]tieno[2,3-b]piridina-3-carboxílico

Se calentaron el Ejemplo 68 (64 mg, 0,13 mmol) y trifenil-fosfina (177 mg, 0,68 mmol) en THF (1 ml) a 65°C durante una noche. Se añadió tricloruro de fósforo (34 mg, 0,39 mmol) y la mezcla de reacción se agitó a la temperatura ambiente durante 90 minutos. Se extinguió la reacción con solución de hidrogenocarbonato de sodio, y el producto se extrajo en DCM, se secó (sulfato de magnesio) y se concentró a vacío. Después de HPLC preparativa, se obtuvo el producto requerido (10 mg) como un sólido blanquecino. δ_H (DMSO-d₆) 9.23 (1H, s), 8.35 (1H, dd, *J* 4.7, 1.6 Hz), 7.84 (1H, dd, *J* 8.1, 1.6 Hz), 7.70 (1H, dd, *J* 10.3, 1.9 Hz), 7.53 (1H, d, *J* 8.4 Hz), 7.37 (1H, dd, *J* 8.1, 4.7 Hz), 7.22 (1H, t, *J* 8.6 Hz), 3.47 (3H, s), 3.20 (3H, s). LCMS (ES⁺) RT 3.23 minutos, 458 (M+H)⁺.

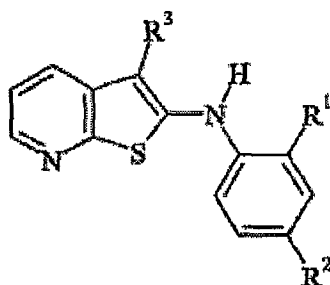
EJEMPLO 70

{2-[(2-Fluoro-4-yodofenil)amino]tieno[2,3-b]piridin-3-il}~[(2R)-2-(hidroximetil)-piperazin-1-il]-metanona

Una solución del Ejemplo 51 (80 mg, 0,13 mmol) en metanol (2 ml) se trató con HCl 4M en 1,4-dioxano (5 ml) y se agitó a t.a. durante 3 h. La mezcla de reacción se concentró a vacío para dar una goma amarilla, que se disolvió en metanol (20 ml) y agua (5 ml), y se alcalinizó luego a pH 11 con hidróxido de amonio aq. al 25%. La solución acuosa se extrajo con DCM (3 x 25 ml), y los extractos orgánicos se reunieron, se secaron (Na_2SO_4), se filtraron y se concentraron a vacío. El producto bruto se sometió a cromatografía en columna (SiO_2 , 95:4:1 DCM/metanol/hidróxido de amonio aq. al 25%) para dar el compuesto del título como una mezcla de dos rotámeros, que se liofilizaron durante una noche en acetonitrilo/agua para dar un polvo de color crema (63 mg, 94%). δ_{H} (DMSO- d_6 , 120°C, contiene rotámeros) 8.37-8.36 (1H, m), 8.29-8.28 (0.44H, m), 8.33 (0.56H, dd, J 1.4, 8.0 Hz), 7.75 (0.44H, dd, J 1.8, 10.0 Hz), 7.68-7.66 (0.44H, m), 7.58 (0.56H, dd, J 1.9, 10.5 Hz), 7.48-7.44 (1H, m), 7.39-7.33 (1H, m), 7.17-7.13 (0.56H, m), 4.31-4.29 (1H, m), 4.00 (1H, m), 3.74-3.60 (2H, m), 3.10-2.83 (3H, m), 2.76-2.65 (2H, m), 2.60-2.53 (1H, m). LCMS RT 2.07 y 1.95 minutos, (ES^+) 513 $(\text{M}+\text{H})^+$.

REIVINDICACIONES

1. Un compuesto de fórmula (I), o una sal farmacéu-
5 camente aceptable, solvato o N-óxido del mismo:



(I)

en donde

R¹ representa hidrógeno, halógeno o alquilo C₁₋₆;

R² representa halógeno o alquilo C₁₋₆;

10 R³ representa hidrógeno, ciano, -CO₂R^a, -CONR^bR^c o -
CON(OR^b)R^c;

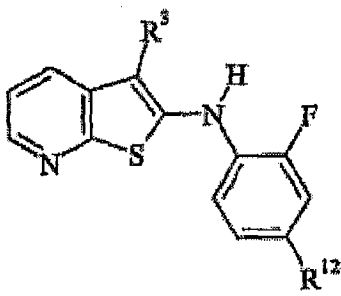
R^a representa alquilo C₁₋₆;

15 R^b representa hidrógeno; o alquilo C₁₋₆, cicloalquilo
C₃₋₇, cicloalquil C₃₋₇-alquilo(C₁₋₆), arilo, aril-
alquilo(C₁₋₆), heterocicloalquilo C₃₋₇, heterocicloalquil
C₃₋₇-alquilo(C₁₋₆), heteroarilo o heteroaril-
alquilo(C₁₋₆), pudiendo estar cualquiera de dichos gru-
pos sustituido opcionalmente con uno o más sustituyen-
tes; y

20 R^c representa hidrógeno o alquilo C₁₋₆ (sustituido
opcionalmente con hidroxilo); o

25 R^b y R^c, cuando se consideran junto con el átomo de
nitrógeno al cual están unidos ambos, representan aze-
tidinilo, pirrolidinilo, piperidinilo, morfolinilo,
tiomorfolinilo, piperazinilo, homopiperidinilo, homo-
morfolinilo u homopiperazinilo, pudiendo estar cual-
quiera de dichos grupos sustituido opcionalmente con
uno o más sustituyentes.

2. Un compuesto de acuerdo con la reivindicación 1, en donde R^b representa hidrógeno; o alquilo C_{1-6} , cicloalquil C_{3-7} -alquilo(C_{1-6}), heterocicloalquil C_{3-7} o heterocicloalquil C_{3-7} -alquilo(C_{1-6}), pudiendo estar cualquiera de dichos grupos sustituido opcionalmente con uno o más sustituyentes.
3. Un compuesto de acuerdo con la reivindicación 1, en donde el resto cíclico $-NR^bR^c$ representa azetidin-1-ilo, pirrolidin-1-ilo, piperidin-1-ilo, morfolin-4-ilo, piperazin-1-ilo u homopiperazin-1-ilo, pudiendo estar cualquiera de dichos grupos sustituido opcionalmente con uno o más sustituyentes.
4. Un compuesto de acuerdo con una cualquiera de las reivindicaciones anteriores, en donde los sustituyentes en R^b , o en el resto cíclico $-NR^bR^c$, se seleccionan de alquilo C_{1-6} , alcoxi C_{1-6} -alquilo(C_{1-6}), hidroxil, hidroxilalquilo(C_{1-6}), amino, amino-alquilo(C_{1-6}), carboximetil, alcoxycarbonil C_{2-6} , alcoxycarbonil C_{2-6} -alquilo(C_{1-6}), di-alquilamino(C_{1-6}), alcoxycarbonilamino C_{2-6} y alcoxycarbonilamino C_{2-6} -alquilo(C_{1-6}).
5. Un compuesto de acuerdo con la reivindicación 1, representado por la fórmula (II), y sales, solvatos y *N*-óxidos farmacéuticamente aceptables del mismo:



(II)

en donde

R^{12} representa halógeno; y

R^3 es como se define en la reivindicación 1.

6. Un compuesto de acuerdo con la reivindicación 5, en donde R¹² representa bromo o yodo.
- 5 7. Un compuesto de acuerdo con la reivindicación 1, como se describe específicamente en esta memoria en uno cualquiera de los ejemplos.
- 10 8. Una composición farmacéutica que comprende un compuesto de fórmula (I) como se define en la reivindicación 1, o una sal, solvato o N-óxido farmacéuticamente aceptable del mismo, en asociación con un vehículo farmacéuticamente aceptable.
- 15 9. El uso de un compuesto de fórmula (I) como se define en la reivindicación 1, o una sal, solvato o N-óxido farmacéuticamente aceptable del mismo, para la fabricación de un medicamento para el tratamiento y/o la prevención de trastornos para los cuales está indicada la
- 20 administración de un inhibidor selectivo de MEK.
- 25 10. Un método para el tratamiento y/o la prevención de trastornos para los cuales está indicada la administración de un inhibidor selectivo de MEK, que comprende administrar a un paciente que se encuentra en necesidad de dicho tratamiento una cantidad eficaz de un compuesto de fórmula (I) como se define en la reivindicación 1, o una sal, solvato o N-óxido farmacéuticamente aceptable del mismo.

From the INTERNATIONAL BUREAU

PCTNOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

THOMPSON, John
UCB Celltech
208 Bath Road
Slough
Berkshire SL1 3WE
ROYAUME-UNI

Date of mailing (day/month/year) 02 March 2007 (02.03.2007)	
Applicant's or agent's file reference G0025-WO01	IMPORTANT NOTIFICATION
International application No. PCT/GB2007/000310	International filing date (day/month/year) 30 January 2007 (30.01.2007)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 31 January 2006 (31.01.2006)
Applicant UCB PHARMA S.A. et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
3. (If applicable) An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
31 January 2006 (31.01.2006)	0601962.4	GB	19 February 2007 (19.02.2007)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Dorothee Mülhausen

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Telephone No. +41 22 338 96 72

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	G0025-WO01
I	Title of invention	THIENO-PYRIDINE DERIVATIVES AS MEK INHIBITORS
II	Applicant	
II-1	This person is	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	UCB PHARMA S.A.
II-5	Address	60 Allée de la Recherche B-1070 Brussels Belgium
II-6	State of nationality	BE
II-7	State of residence	BE
II-8	Telephone No.	+32 2 559 9999
II-9	Facsimile No.	+32 2 559 9900

PCT REQUEST

Original (for SUBMISSION)

III-1	Applicant and/or Inventor	
III-1-1	This person is	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	HUTCHINGS, Martin Clive
III-1-5	Address	UCB Celltech 208 Bath Road Slough Berkshire SL1 3WE 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)	ARCHIBALD, Sarah Catherine
III-2-5	Address	UCB Celltech 208 Bath Road Slough Berkshire SL1 3WE 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)	BROOKINGS, Daniel Christopher
III-3-5	Address	UCB Celltech 208 Bath Road Slough Berkshire SL1 3WE United Kingdom
III-3-6	State of nationality	GB
III-3-7	State of residence	GB

PCT REQUEST

Original (for SUBMISSION)

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)	DAVIS, Jeremy Martin
III-4-5	Address	UCB Celltech 208 Bath Road Slough Berkshire SL1 3WE United Kingdom
III-4-6	State of nationality	GB
III-4-7	State of residence	GB
III-5	Applicant and/or Inventor	
III-5-1	This person is	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	JOHNSON, James Andrew
III-5-5	Address	UCB Celltech 208 Bath Road Slough Berkshire SL1 3WE United Kingdom
III-5-6	State of nationality	GB
III-5-7	State of residence	GB
III-6	Applicant and/or Inventor	
III-6-1	This person is	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	LANGHAM, Barry John
III-6-5	Address	UCB Celltech 208 Bath Road Slough Berkshire SL1 3WE United Kingdom
III-6-6	State of nationality	GB
III-6-7	State of residence	GB

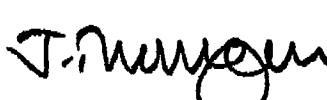
PCT REQUEST

Original (for SUBMISSION)

III-7	Applicant and/or inventor	applicant and inventor US only NEUSS, Judi Charlotte UCB Celltech 208 Bath Road Slough Berkshire SL1 3WE United Kingdom
III-7-1	This person is	
III-7-2	Applicant for	
III-7-4	Name (LAST, First)	
III-7-5	Address	
III-7-6	State of nationality	GB
III-7-7	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 (LAST, First)	THOMPSON, John
IV-1-2	Address	UCB Celltech 208 Bath Road Slough Berkshire SL1 3WE United Kingdom
IV-1-3	Telephone No.	+44 1753 442193
IV-1-4	Facsimile No.	+44 1753 447895
IV-1-5	e-mail	john.thompson@ucb-group.com
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	31 January 2006 (31.01.2006)
VI-1-2	Number	0601962.4
VI-1-3	Country	GB

PCT REQUEST

Original (for SUBMISSION)

VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	6	✓
IX-2	Description	54	-
IX-3	Claims	3	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	64	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-17	PCT-SAFE physical media	-	✓
IX-18	other	Form 23/77	
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST, First)	THOMPSON, John	
X-1-2	Name of signatory		
X-1-3	Capacity		

PCT REQUEST

Original (for SUBMISSION)

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

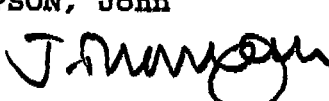
FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION)

(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	
0-4	Form PCT/RO/101 (Annex)	
0-4-1	PCT Fee Calculation Sheet Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.163)
0-9	Applicant's or agent's file reference	
2	Applicant	
12	Calculation of prescribed fees	
12-1	Transmittal fee T	⇒ 55
12-2-1	Search fee S	⇒ 1098
12-2-2	International search to be carried out by	EP
12-3	International filing fee (first 30 sheets) I1	611
12-4	Remaining sheets	34
12-5	Additional amount (X) 7	
12-6	Total additional amount I2	238
12-7	I1 + I2 = I	849
12-12	EASY Filing reduction R	-44
12-13	Total international filing fee (I-R) I	⇒ 805
12-14	Fee for priority document	
	Number of priority documents requested	1
12-15	Fee per document (X) 22	
12-16	Total priority document fee: P	⇒ 22
12-17	TOTAL FEES PAYABLE (T+S+I+P)	⇒ 1980
12-19	Mode of payment	
12-20	authorization to charge deposit account	
12-20	Deposit account instructions	
	The receiving Office	United Kingdom Patent Office (RO/GB)
12-20-1	Authorization to charge the total fees indicated above	✓
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above	✓
12-20-3	Authorization to charge the fee for priority document	✓
12-21	Deposit account No.	
	D02494	
12-22	Date	
	30 January 2007 (30.01.2007)	
12-23	Name and signature	
	THOMPSON, John 	

150
30012
45.103078

Brigard & Castro
BOGOTA - COLOMBIA

PODER

Yo (nosotros) **UCB PHARMA, S.A.**

domiciliado(s) en 60, Allée de la Recherche, B-1070 Bruselas, Bélgica

Nombro(amos) a: **JUAN PABLO CADENA SARMIENTO** y/o **CARLOS H. PALACIO EASTMAN** y/o **MARTIN E. TORRES CARDOZO**, 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, lemas comerciales y enseññas, 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, domicilio y/o dirección; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo, (nosotros) a: **JUAN PABLO CADENA SARMIENTO** y/o **CARLOS H. PALACIO EASTMAN** y/o **MARTIN E. TORRES CARDOZO**, domiciliado(s) en la 7 No. 71-21, Torre B, Piso 4, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales y extrajudiciales.

Otorgado y firmado en Bruselas

hoy de de

POWER OF ATTORNEY

I (We) **UCB PHARMA, S.A.**

domiciled in 60, Allée de la Recherche, B-1070 Brussels, Belgium

Hereby appoints **JUAN PABLO CADENA SARMIENTO** and/or **CARLOS H. PALACIO EASTMAN** and/or **MARTIN E. TORRES CARDOZO**, 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, slogans 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, domicile and/or address 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 exploitation of licenses, action of unfair competition; criminal proceedings, actions for payment of 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 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 kinds 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 (We) hereby appoint **JUAN PABLO CADENA SARMIENTO** and/or **CARLOS H. PALACIO EASTMAN** and/or **MARTIN E. TORRES CARDOZO**, domiciled in Carrera 7 No. 71-21, Torre B, Piso 4, my (our) attorney(s) in fact, with powers to receive notifications and designate judicial and extrajudicial attorneys.

Granted and signed in Brussels

10th day of July 2007

NOTARIO
ALEXANDER CUARENTA
200. Aguacatal
Castillo Zárate

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy de de
personalmente compareció ante mí Allen NORRIS

a quien conozco, y de quien me consta que firmó el anterior documento, debidamente juramentado declaró y dijo que él (ella) es el Apoderado y Representante Legal

de UCB PHARMA, S.A.

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 objeto social 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(eron) ante mí

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) declara(n) que otorgan el mismo para fines y propósitos que en él se expresan.

Notario Público (sello)

NOTARIAL CERTIFICATE (CORPORATION)

On this 20th day of July of 2007 personally appeared before me Allen NORRIS

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 Proxy and Legal Representative

of UCB PHARMA, S.A.

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 the purpose for which this instrument is granted is 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 Brussels
under date of 20 July 2007

and that he (she) who grants the present power of attorney is its Representative.



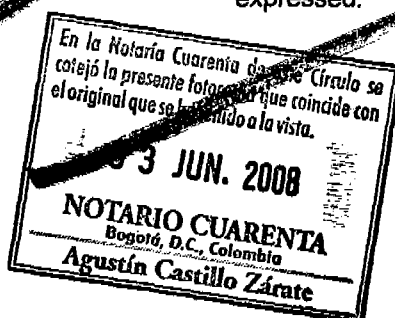
Damien HISSETTE
Notaire associé à Bruxelles
Rue de l'Association 30 Verenigingstraat
Bruxelles 1000 Brussel

**NOTARIAL CERTIFICATE
NATURAL PERSON**

On this day of personally appeared before me

who is(are) known to me and who I attest executed the foregoing document and he (they) declared he (they) grant(s) the document for the uses and purposes therein expressed.

Notary Public (Seal)



152 152

TRADUCCION AL ESPAÑOL del Documento de Poder otorgado por UCB
PHARMA, S.A., con domicilio en Allée de la Recherche 60 B – 1070 Bruselas,
Bélgica.

Hay un sello que dice:

ALLEN NORRIS
Apoderado y representante legal

Hay un sello que dice:

Damien Hisette
Notario Asociado – Geassocieerde notaris
Rue de l'Association 30 Verenigingstraat
Bruxelles 1000 Bruselas

Hay un sello que dice:

Damien Hisette
Notario Asociado de Bruselas
Geassocieerde notaris et Brussel

APOSTILLA
(Convención de la Haya de Octubre 5 de 1961)

1. País: Bélgica

Este documento público

2. ha sido firmado por: Hisette, Damien

3. actuando en capacidad de: Notario

4. lleva el sello/timbre de: Notario
Bruselas

Certificado

5. en Bruselas

6. El: 29/07/2007

7. por el Servicio Público federal de Asuntos extranjeros, Comercio exterior y
Cooperación para el Desarrollo

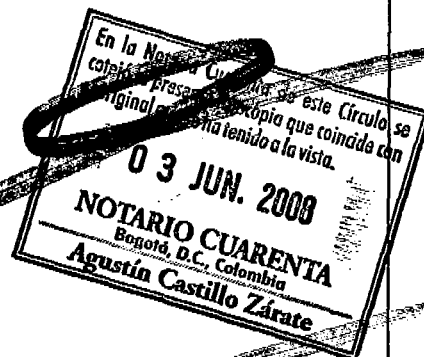
8. No. 9805070720744644

9. Sello/timbre:
hay un sello que dice:

10. Firma

SERVICIO PÚBLICO FEDERAL
DE ASUNTOS EXTRANJEROS
COMERCIO EXTERIOR Y COO-
PERACION PARA EL DESARROLLO

(FIRMA)
Jean-Paul Lignier





No. 08-080917- -00000-0000

Fecha: 2008-08-04 17:03:26 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eva: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 152



Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION

MODELO DE UTILIDAD []

- ◆ Indicación de que se solicita la concesión de una patente
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ◆ Descripción de la invención
- ◆ Dibujos de ser estos pertinentes
- ◆ Comprobante de pago de las tasas establecidas

COMPLETA []

INCOMPLETA []

DISEÑO INDUSTRIAL []

- ◆ Indicación 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

Carrera 13 No. 27-00 Piso 6, 7 y 10

Corredor: 3 82 08 40

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CADENA SARMIENTO JUAN PABLO
Apoderado(a) y/o Representante de
UCB PHARMA S.A.

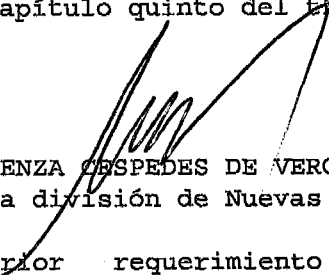
REFERENCIA	Radicación No.	8 80917
	Solicitud internacional	PCT/GB2007/000310
	Fecha inicio fase nacional	31/08/2008
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	- 12161

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No.10 de 2001.


ALIX CARMENZA OSPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de
fecha 26 SET. 2008
adpall