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Organización y
Digitalización USA Ltda



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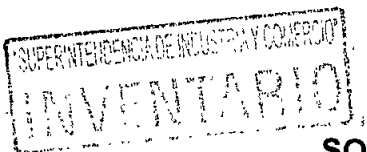
Industria y Comercio

SUPERINTENDENCIA

10-74471

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES



SOLICITUD DE PATENTE DE
INVENCION

TITULO: DERIVADOS DE OXADIAZOL ACTIVOS
EN 1- FOSFATO DE ESFINGOSINA.

SOLICITANTE: GLAXO GROUP LIMITED.

DIRECCIÓN: Glaxo Wellcome House, Berkeley Avenue, Greenford,
Middlesex UB6 ONN. Inglaterra

APODERADO: CARLOS R. OLARTE

BOGOTÁ Junio de 2009

P2010/000082

91202-2000

OLARTE RAISBECK

OLARTE RAISBECK MOURE & C^{IA}



Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-074471-00000-0000

Fecha: 2010-06-21 17:06:21 Dep: 2020 DIR NUEVASCR
Tra: 11 PATENTEIYII Eve: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 169

PETITORIO - FORMULARIO

PATENTE PCT

ENTRADA EN FASE NACIONAL

P2010/000082

SOLICITUD DE:

1

☒

Patente de Invención.

☐

Patente de Modelo de Utilidad.

☐

Capítulo I.

☒

Capítulo II.

2

SOLICITANTE
(71)

Nombre: GLAXO GROUP LIMITED

Dirección: Glaxo Wellcome House, Berkeley Avenue, Greenford Middlesex UB6 0NN

Nacionalidad o Domicilio: Estadounidense

Lugar de Constitución: Estados Unidos de América.

Teléfono: _____ Fax: _____

E-mail: _____

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

REPRESENTANTE
O APODERADO

Nombre: CARLOS R. OLARTE

Dirección: Diagonal 34 No. 5-28 Bogotá, D.C.

Teléfono: 601-7700 Fax: 601-7799

E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número 79782747Bta
TP 74.295

INVENTOR (ES)
(72)

Nombre: 1) JAG PAUL HEER 2) THOMAS DANIEL HEIGHTMAN

Dirección: 1) y 2) GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5 AW

Nacionalidad o Domicilio: 1) y 2) Británica

5

PCT (86)

Solicitud Internacional No. PCT/EP2008/067963 Fecha Diciembre 19, 2008

Publicación Internacional No. WO 2009/080724 Fecha Julio 02, 2009

6

Título (54) DERIVADOS DE OXADIAZOL ACTIVOS EN 1-FOSFATO DE ESFINGOSINA

Clasificación Internacional (51) C07D 413/04, C07D 217/06, C07D 217/22, C07D 217/16, A61P 37/00, A61P 17/00, A61K 31/4725, C07D 413/14

Prioridad
SI ☒ NO ☐

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GB

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Diciembre 21, 2007

(31) Número de Solicitud

0725101.0

9

Comprobante de pago No. 10-

Fecha Junio 21 de 2010

10

ANEXOS

2

☒

Comprobante de pago de la tasa de presentación de la solicitud.

☒

Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.

☒

Poderes, si fuere el caso. Adjunto copia simple ver Expediente No.

☐

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 internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).

☐

Traducción del examen preliminar internacional 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 12 x 12.

☐

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.

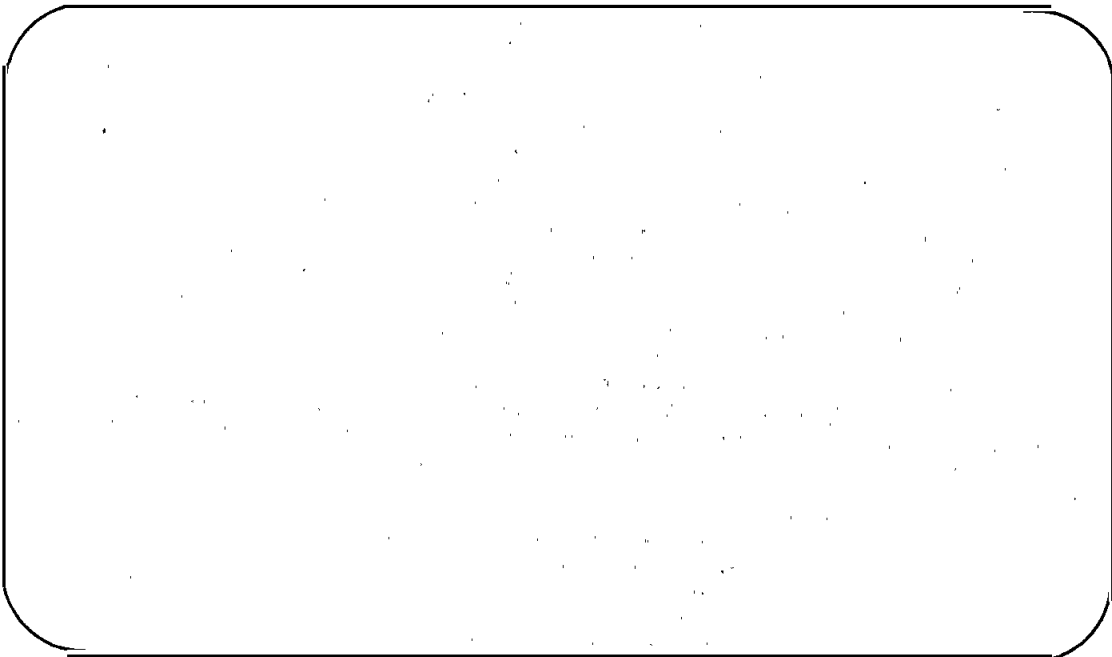
☐

De ser el caso, modificaciones efectuadas a la solicitud internacional.

☒

Otros. Búsqueda Internacional

11

FIGURA CARACTERÍSTICA:☐

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTEC.C. 79.782.747 Bta T.P. 74.295

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-074471- -00000-0000

Fecha: 2010-06-21 17:06:21 Dep. 2020 DIR NUEVASCR
Tra. 11 PATENTEIYII Eve. 379 FASENACIONALII
Act. 411 PRESENTACION Folios 169

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 300176089-2

RECIBO OFICIAL DE CAJA • 10 - 49,660
FECHA : JUNIO 21 DE 2010

***V CONSTANCIA ***V

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VAL. PAGO
BLARTE PATENSEY	CONSIGNACION	BANCO DE SOCOTA	062754387	174655226	21/06/2010	7,858,000.00

***V CONCEPTO ***V

CANT. PATENTISTAS	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITE DE SOL. DE PATENTE DE IN	554,000.00
	TOTAL :	554,000.00

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

**APOSTILLA EN PODER DE REPRESENTACIÓN DE
GLAXO GROUP LIMITED**

PODER DE REPRESENTACION

Bilingüe inglés- español otorgado en Brentford, Middlesex, Inglaterra el 13 de agosto de 2003 y firmado por Peter John Giddings, Apoderado y Funcionario autorizado.

Certificado de Notario De Pinna en español firmado por James Kerr Milligan

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
- Este documento Público
2. ha sido firmado por James Kerr Milligan
3. Quien ejerce funciones de Notario público
4. Lleva el sello del Notario público

CERTIFICADO

5. En Londres
6. El 14 agosto 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la Mancomunidad
8. No. G229474
9. Gran Sello de la Oficina de Asuntos exteriores y de la Mancomunidad
10. Firma legible de J. Garbrah- Por el Secretario de Estado

Si el documento se usa en un país que no pertenece a la Convención de la Haya del 5 de octubre de 1961 debe pasar por la sección consular de la Misión que representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 21 agosto-03.

Marlen Neira C


MARLEN NEIRA CASTRO
Traductor e Intérprete Ofi.
Inglés - Español - Inglés
Resolución No. 2117 del 7 O.

Yo, el infrascrito **JAMES KERR MILLIGAN**, Notario Público de la Ciudad de Londres, Inglaterra, por la Autoridad Real debidamente admitido y juramentado,

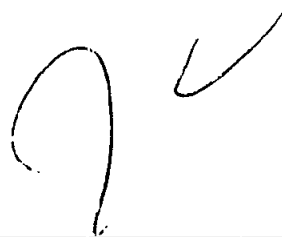
C E R T I F I C O:

QUE es auténtica la firma suscrita al pie del adjunto Poder, por ser del puño y letra del Señor Don **PETER JOHN GIDDINGS**, cuya identidad me consta, Apoderado de la Sociedad inglesa denominada "**GLAXO GROUP LIMITED**", Sociedad legalmente constituida y existente de acuerdo con las leyes de Inglaterra, e inscrita en la Oficina de Registro de Sociedades bajo el número **305979**, con domicilio social en Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN, Inglaterra;

QUE el citado Señor Don **PETER JOHN GIDDINGS** está debidamente autorizado para firmar documentos de esta clase en nombre y representación de dicha Sociedad en virtud de un Poder otorgado por la referida Sociedad fechado 3 de julio de 2002.

Y QUE los objetos para los cuales se otorgó dicho Poder se encuentran dentro de los objetos o actividades de la citada Sociedad, de acuerdo con la Escritura Constitutiva y los Estatutos Sociales, los cuales he tenido a la vista.

Y PARA QUE CONSTE donde y como convenga y fuere necesario expido el presente Certificado que firmo y sello en dicha Ciudad de Londres, el día de hoy trece de agosto del año dos mil tres.



JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra



...6

APOSTILLE

(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le présent acte public

2. Has been signed by **James Kerr Milligan**
a été signé par
3. Acting in the capacity of **Notary Public**
agissant en qualité de
4. Bears the seal/stamp of **The Said Notary Public**
est revêtu du sceau/timbre de

Certified/Attesté

5. at London/à Londres
6. the/le **14 August 2003**
7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **G229474**

9. Stamp:
timbre:
10. Signature: **J. Garbrah**



For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961,
it should be presented to the consular section of the mission representing that country.

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
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Power of Attorney

The undersigned,

domiciled in

Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, GB
by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents, Utility Models and Industrial Designs** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

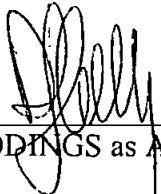
Poder

El suscrito,

domiciliado en

Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, GB
por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de **Patentes, Modelos de Utilidad y Diseños Industriales** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:


Peter John GIDDINGS as Attorney and Authorised Official

Date/Fecha: 13 August 2003

City, Country/Ciudad, País: Brentford, Middlesex, England

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
2 July 2009 (02.07.2009)

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(10) International Publication Number
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(51) International Patent Classification:

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C07D 217/22 (2006.01) A61K 31/4725 (2006.01)
C07D 217/16 (2006.01) C07D 413/14 (2006.01)

(21) International Application Number:

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(22) International Filing Date:

19 December 2008 (19.12.2008)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

0725101.0 21 December 2007 (21.12.2007) GB

(71) Applicant (for all designated States except US): **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **HEER, Jag, Paul** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **HEIGHTMAN, Thomas, Daniel** [GB/GB]; c/o Glaxo-SmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB).

(74) Agents: **GRIFFITH, Johanna, Elise et al.**; Glaxo-SmithKline, Corporate Intellectual Property CN925.1, 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

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

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

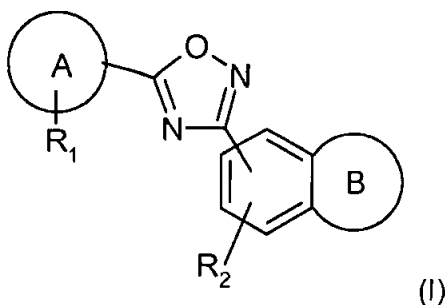
Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- of inventorship (Rule 4.17(iv))

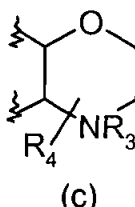
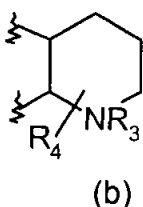
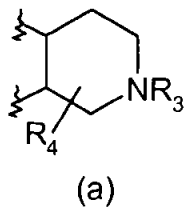
Published:

- with international search report

(54) Title: OXADIAZOLE DERIVATIVES ACTIVE ON SPHINGOSINE-1-PHOSPHATE (S1P)



(57) Abstract: The present application discloses oxadiazole based compounds of Formula (I) active on sphingosine-1-phosphate (S1P) in particular useful to treat lupus erythematosus. A is phenyl or a 5 or 6-membered heteroaryl ring; B is selected from one of the following; Formulae: (a) (b) (c)



OXADIAZOLE DERIVATIVES ACTIVE ON SPHINGOSINE-1-PHOSPHATE (S1P)

The present invention relates to novel oxadiazole derivatives having pharmacological activity, processes for their preparation, pharmaceutical compositions containing
5 them and their use in the treatment of various disorders.

Sphingosine 1-phosphate (S1P) is a bioactive lipid mediator formed by the phosphorylation of sphingosine by sphingosine kinases and is found in high levels in the blood. It is produced and secreted by a number of cell types, including those of
10 hematopoietic origin such as platelets and mast cells (Okamoto *et al* 1998 J Biol Chem 273(42):27104; Sanchez and Hla 2004, J Cell Biochem 92:913). It has a wide range of biological actions, including regulation of cell proliferation, differentiation, motility, vascularisation, and activation of inflammatory cells and platelets (Pyne and Pyne 2000, Biochem J. 349: 385). Five subtypes of S1P responsive receptor have
15 been described, S1P1 (Edg-1), S1P2 (Edg-5), S1P3 (Edg-3), S1P4 (Edg-6), and S1P5 (Edg-8), forming part of the G-protein coupled endothelial differentiation gene family of receptors (Chun *et al* 2002 Pharmacological Reviews 54:265, Sanchez and Hla 2004 J Cellular Biochemistry, 92:913). These 5 receptors show differential mRNA expression, with S1P1-3 being widely expressed, S1P4 expressed on
20 lymphoid and hematopoietic tissues and S1P5 primarily in brain and to a lower degree in spleen. They signal via different subsets of G proteins to promote a variety of biological responses (Kluk and Hla 2002 Biochem et Biophysica Acta 1582:72, Sanchez and Hla 2004, J Cellular Biochem 92:913).

Proposed roles for the S1P1 receptor include lymphocyte trafficking, cytokine induction/suppression and effects on endothelial cells (Rosen and Goetzl 2005 Nat Rev Immunol. 5:560). Agonists of the S1P1 receptor have been used in a number of autoimmune and transplantation animal models, including Experimental Autoimmune Encephalomyelitis (EAE) models of MS, to reduce the severity of the induced disease
30 (Brinkman *et al* 2003 JBC 277:21453; Fujino *et al* 2003 J Pharmacol Exp Ther 305:70; Webb *et al* 2004 J Neuroimmunol 153:108; Rausch *et al* 2004 J Magn Reson Imaging 20:16). This activity is reported to be mediated by the effect of S1P1 agonists on lymphocyte circulation through the lymph system. Treatment with S1P1 agonists results in the sequestration of lymphocytes within secondary lymphoid
35 organs such as the lymph nodes, inducing a reversible peripheral lymphopenia in animal models (Chiba *et al* 1998, J Immunology 160:5037, Forrest *et al* 2004 J



Pharmacol Exp Ther 309:758; Sanna et al 2004 JBC 279:13839). Published data on agonists suggests that compound treatment induces loss of the S1P1 receptor from the cell surface via internalisation (Graler and Goetzl 2004 FASEB J 18:551; Matloubian et al 2004 Nature 427:355; Jo et al 2005 Chem Biol 12:703) and it is this
5 reduction of S1P1 receptor on immune cells which contributes to the reduction of movement of T cells from the lymph nodes back into the blood stream.

S1P1 gene deletion causes embryonic lethality. Experiments to examine the role of the S1P1 receptor in lymphocyte migration and trafficking have included the adoptive
10 transfer of labelled S1P1 deficient T cells into irradiated wild type mice. These cells showed a reduced egress from secondary lymphoid organs (Matloubian et al 2004 Nature 427:355).

S1P1 has also been ascribed a role in endothelial cell junction modulation (Allende et al 2003 102:3665, Blood Singelton et al 2005 FASEB J 19:1646). With respect to
15 this endothelial action, S1P1 agonists have been reported to have an effect on isolated lymph nodes which may be contributing to a role in modulating immune disorders. S1P1 agonists caused a closing of the endothelial stromal 'gates' of lymphatic sinuses which drain the lymph nodes and prevent lymphocyte egress (Wei
20 wt al 2005, Nat. Immunology 6:1228).

The immunosuppressive compound FTY720 (JP11080026-A) has been shown to reduce circulating lymphocytes in animals and man, have disease modulating activity in animal models of immune disorders and reduce remission rates in relapsing
25 remitting Multiple Sclerosis (Brinkman et al 2002 JBC 277:21453, Mandala et al 2002 Science 296:346, Fujino et al 2003 J Pharmacology and Experimental Therapeutics 305:45658, Brinkman et al 2004 American J Transplantation 4:1019, Webb et al 2004 J Neuroimmunology 153:108, Morris et al 2005 EurJ Immunol 35:3570, Chiba 2005 Pharmacology and Therapeutics 108:308, Kahan et al 2003, Transplantation
30 76:1079, Kappos et al 2006 New Eng J Medicine 335:1124). This compound is a prodrug that is phosphorylated in vivo by sphingosine kinases to give a molecule that has agonist activity at the S1P1, S1P3, S1P4 and S1P5 receptors. Clinical studies have demonstrated that treatment with FTY720 results in bradycardia in the first 24 hours of treatment (Kappos et al 2006 New Eng J Medicine 335:1124). The
35 bradycardia is thought to be due to agonism at the S1P3 receptor, based on a number of cell based and animal experiments. These include the use of S1P3 knock-

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out animals which, unlike wild type mice, do not demonstrate bradycardia following FTY720 administration and the use of S1P1 selective compounds (Hale et al 2004 Bioorganic & Medicinal Chemistry Letters 14:3501, Sanna et al 2004 JBC 279:13839, Koyrakh et al 2005 American J Transplantation 5:529).

5

Hence, there is a need for S1P1 receptor agonist compounds with selectivity over S1P3 which might be expected to show a reduced tendency to induce bradycardia.

The following patent applications describe oxadiazole derivatives as S1P1 agonists:

10 WO03/105771, WO05/058848, WO06/047195, WO06/100633, WO06/115188, WO06/131336, WO07/024922 and WO07/116866.

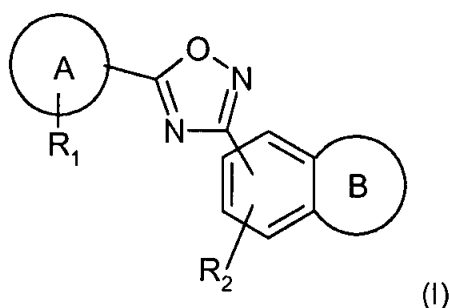
The following patent applications describe tetrahydroisoquinolinyl-oxadiazole derivatives as S1P receptor agonists: WO06/064757, WO06/001463, WO04/113330.

15

A structurally novel class of compounds has now been found which provides agonists of the S1P1 receptor.

The present invention therefore provides compounds of formula (I) or a pharmaceutically acceptable salt thereof thereof:

20



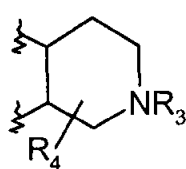
A is phenyl or a 5 or 6-membered heteroaryl ring;

25 R₁ is up to two substituents independently selected from halogen, C₍₁₋₃₎alkoxy, C₍₁₋₃₎fluoroalkyl, cyano, C₍₁₋₃₎fluoroalkoxy, C₍₁₋₆₎alkyl and C₍₃₋₆₎cycloalkyl;

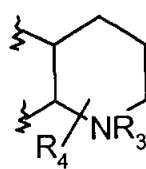
R₂ is hydrogen, halogen or C₍₁₋₄₎alkyl;

B is selected from one of the following:

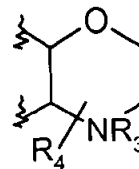
12



(a)



(b)



(c)

R_3 is hydrogen, $C_{(1-3)}$ alkyl or $(CH_2)_{1-3}CO_2H$;

R_4 is hydrogen or $C_{(1-3)}$ alkyl;

when R_2 or R_4 is alkyl it may be optionally interrupted by oxygen.

5

In one embodiment of the invention,

A is phenyl; and/or

R_1 is up to two substituents independently selected from chloro, isopropoxy, and cyano; and/or

10

R_2 is hydrogen; and/or

B is (a); and/or

R_3 is hydrogen, methyl or $(CH_2)_{1-3}CO_2H$; and/or

R_4 is hydrogen.

15

A is phenyl;

R_1 is up to two substituents independently selected from chloro, isopropoxy, and cyano;

R_2 is hydrogen or methyl ;

B is (a);

20

R_3 is hydrogen, methyl or $(CH_2)_{1-3}CO_2H$;

R_4 is hydrogen.

In one embodiment A is phenyl. In another embodiment A is 3,4-disubstituted phenyl.

25 In one embodiment R_1 is two substituents one of which is $C_{(1-3)}$ alkoxy, the other selected from halogen or cyano. In another embodiment R_1 is two substituents, one of which is isopropoxy and the other is selected from chloro or cyano. In another embodiment R_1 is two substituents selected from chloro, isopropoxy and cyano. In another embodiment R_1 is chloro and isopropoxy. In a further embodiment R_1 is chloro at the 3-position and isopropoxy at the 4-position when A is phenyl. In another embodiment R_1 is isopropoxy and cyano. In a further embodiment R_1 is cyano at the 3-position and isopropoxy at the 4-position when A is phenyl.

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In one embodiment R_2 is hydrogen or methyl.

In one embodiment B is (a).

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In one embodiment R_3 is hydrogen, methyl or $(CH_2)_{1-3}CO_2H$.

In one embodiment R_4 is hydrogen.

- 10 The term "alkyl" as a group or part of a group e.g. alkoxy or hydroxyalkyl refers to a straight or branched alkyl group in all isomeric forms. The term " $C_{(1-6)}$ alkyl" refers to an alkyl group, as defined above, containing at least 1, and at most 6 carbon atoms. Examples of such alkyl groups include methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, or *tert*-butyl. Examples of such alkoxy groups include methoxy, 15 ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, *sec*-butoxy and *tert*-butoxy.

Suitable $C_{(3-6)}$ cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

- 20 As used herein, the term "halogen" refers to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I) and the term "halo" refers to the halogen: fluoro (-F), chloro (-Cl), bromo(-Br) and iodo(-I).

- The term "heteroaryl" represents an unsaturated ring which comprises one or more 25 heteroatoms selected from O, N or S. Examples of 5 or 6 membered heteroaryl rings include pyrrolyl, triazolyl, thiadiazolyl, tetrazolyl, imidazolyl, pyrazolyl, isothiazolyl, thiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, furazanyl, furanyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl.

- 30 In certain of the compounds of formula (I), dependent upon the nature of the substituent there are chiral carbon atoms and therefore compounds of formula (I) may exist as stereoisomers. The invention extends to all optical isomers such as stereoisomeric forms of the compounds of formula (I) including enantiomers, diastereoisomers and mixtures thereof, such as racemates. The different 35 stereoisomeric forms may be separated or resolved one from the other by

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conventional methods or any given isomer may be obtained by conventional stereoselective or asymmetric syntheses.

Certain of the compounds herein can exist in various tautomeric forms and it is to be understood that the invention encompasses all such tautomeric forms.

It is understood that certain compounds of the invention contain both acidic and basic groups and may therefore exist as zwitterions at certain pH values.

10 Suitable compounds of the invention are:

5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,3,4-tetrahydroisoquinoline

15 2-[(1-methylethyl)oxy]-5-[3-(1,2,3,4-tetrahydro-5-isoquinoliny)-1,2,4-oxadiazol-5-yl]benzonitrile

[5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1H)-isoquinoliny]acetic acid

20 3-[5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1H)-isoquinoliny]propanoic acid

4-[5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1H)-isoquinoliny]butanoic acid

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2-[(1-methylethyl)oxy]-5-[3-(2-methyl-1,2,3,4-tetrahydro-5-isoquinoliny)-1,2,4-oxadiazol-5-yl]benzonitrile

30 [8-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2H-chromen-4-yl]acetic acid

3-[6-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinoliny]propanoic acid

35 [6-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinoliny]acetic acid

6-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-1,2,3,4-tetrahydroisoquinoline

2-[(1-Methylethyl)oxy]-5-[3-(5-methyl-1,2,3,4-tetrahydro-6-isoquinoliny)-1,2,4-oxadiazol-5-yl]benzonitrile

[6-(5-{3-Cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinoliny]acetic acid

3-[6-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinoliny]propanoic acid

or pharmaceutically acceptable salts thereof.

Pharmaceutically acceptable derivatives of compounds of formula (I) include any pharmaceutically acceptable salt, ester or salt of such ester of a compound of formula (I) which, upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

The compounds of formula (I) can form salts. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

Salts may also be prepared from pharmaceutically acceptable bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Salts derived from pharmaceutically acceptable organic bases include salts of primary, secondary, and tertiary amines; substituted amines including naturally occurring substituted amines; and cyclic amines. Particular pharmaceutically acceptable organic bases

include arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, 5 piperazine, piperidine, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tris(hydroxymethyl)aminomethane (TRIS, trometamol) and the like. Salts may also be formed from basic ion exchange resins, for example polyamine resins. When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable acids, including inorganic and organic acids. Such 10 acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, ethanedisulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, pamoic, pantothenic, phosphoric, propionic, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like.

15 Pharmaceutically acceptable addition salts may be prepared conventionally by reaction with the appropriate acid or acid derivative. Pharmaceutically acceptable salts with bases may be prepared conventionally by reaction with the appropriate inorganic or organic base.

20 The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. This invention includes within its scope stoichiometric hydrates or solvates as well as compounds containing 25 variable amounts of water and/or solvent.

Included within the scope of the invention are all salts, solvates, hydrates, complexes, polymorphs, prodrugs, radiolabelled derivatives, stereoisomers and optical isomers of the compounds of formula (I).

30 The potencies and efficacies of the compounds of this invention for the S1P1 receptor can be determined by GTPyS assay performed on the human cloned receptor as described herein. Compounds of formula (I) have demonstrated agonist activity at the S1P1 receptor, using functional assays described herein.

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Compounds of formula (I) and their pharmaceutically acceptable salts are therefore of use in the treatment of conditions or disorders which are mediated via the S1P1 receptor. In particular the compounds of formula (I) and their pharmaceutically acceptable salts are of use in the treatment of multiple sclerosis, autoimmune diseases, chronic inflammatory disorders, asthma, inflammatory neuropathies, arthritis, transplantation, Crohn's disease, ulcerative colitis, lupus erythematosus, psoriasis, ischemia-reperfusion injury, solid tumours, and tumour metastasis, diseases associated with angiogenesis, vascular diseases, pain conditions, acute viral diseases, inflammatory bowel conditions, insulin and non-insulin dependant diabetes (herein after referred to as the "Disorders of the Invention").

Compounds of formula (I) and their pharmaceutically acceptable salts are therefore of use in the treatment of lupus erythematosus.

Compounds of formula (I) and their pharmaceutically acceptable salts are therefore of use in the treatment of psoriasis.

Compounds of formula (I) and their pharmaceutically acceptable salts are therefore of use in the treatment of multiple sclerosis.

It is to be understood that "treatment" as used herein includes prophylaxis as well as alleviation of established symptoms.

Thus the invention also provides compounds of formula (I) or pharmaceutically acceptable salts thereof, for use as therapeutic substances, in particular in the treatment of the conditions or disorders mediated via the S1P1 receptor. In particular the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as a therapeutic substance in the treatment of multiple sclerosis, autoimmune diseases, chronic inflammatory disorders, asthma, inflammatory neuropathies, arthritis, transplantation, Crohn's disease, ulcerative colitis, lupus erythematosus, psoriasis, ischemia-reperfusion injury, solid tumours, and tumour metastasis, diseases associated with angiogenesis, vascular diseases, pain conditions, acute viral diseases, inflammatory bowel conditions, insulin and non-insulin dependant diabetes.

Compounds of formula (I) and their pharmaceutically acceptable salts are of use as therapeutic substances in the treatment of lupus erythematosus.

Compounds of formula (I) and their pharmaceutically acceptable salts are of use as
5 therapeutic substances in the treatment of psoriasis.

Compounds of formula (I) and their pharmaceutically acceptable salts are of use as therapeutic substances in the treatment of multiple sclerosis.

10 The invention further provides a method of treatment of conditions or disorders in mammals including humans which can be mediated via the S1P1 receptor, which comprises administering to the sufferer a therapeutically safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. In particular the invention provides a method of treatment of multiple sclerosis, autoimmune
15 diseases, chronic inflammatory disorders, asthma, inflammatory neuropathies, arthritis, transplantation, Crohn's disease, ulcerative colitis, lupus erythematosus, psoriasis, ischemia-reperfusion injury, solid tumours, and tumour metastasis, diseases associated with angiogenesis, vascular diseases, pain conditions, acute viral diseases, inflammatory bowel conditions, insulin and non-insulin dependant
20 diabetes, which comprises administering to the sufferer a therapeutically safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The invention provides a method of treatment of lupus erythematosus, which
25 comprises administering to the sufferer a therapeutically safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The invention provides a method of treatment of psoriasis, which comprises administering to the sufferer a therapeutically safe and effective amount of a
30 compound of formula (I) or a pharmaceutically acceptable salt thereof.

The invention provides a method of treatment of multiple sclerosis, which comprises administering to the sufferer a therapeutically safe and effective amount of a
35 compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides for the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of the conditions or disorders mediated via the S1P1 receptor.

- 5 In particular the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the manufacture of a medicament for use in the treatment of multiple sclerosis, autoimmune diseases, chronic inflammatory disorders, asthma, inflammatory neuropathies, arthritis, transplantation, Crohn's disease, ulcerative colitis, lupus erythematosus, psoriasis, ischemia-reperfusion
- 10 injury, solid tumours, and tumour metastasis, diseases associated with angiogenesis, vascular diseases, pain conditions, acute viral diseases, inflammatory bowel conditions, insulin and non-insulin dependant diabetes.

- Compounds of formula (I) and their pharmaceutically acceptable salts are of use in
- 15 the manufacture of a medicament for use in the treatment of lupus erythematosus.

Compounds of formula (I) and their pharmaceutically acceptable salts are of use in the manufacture of a medicament for use in the treatment of psoriasis.

- 20 Compounds of formula (I) and their pharmaceutically acceptable salts are of use in the manufacture of a medicament for use in the treatment of multiple sclerosis.

- In order to use the compounds of formula (I) and pharmaceutically acceptable salts thereof in therapy, they will normally be formulated into a pharmaceutical
- 25 composition in accordance with standard pharmaceutical practice. The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

- 30 In a further aspect, the present invention provides a process for preparing a pharmaceutical composition, the process comprising mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

- 35 A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for

oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

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Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); tableting lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); and acceptable wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats), emulsifying agents (e.g. lecithin or acacia), non-aqueous vehicles (which may include edible oils e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils), preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid), and, if desired, conventional flavourings or colorants, buffer salts and sweetening agents as appropriate. Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

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For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salts thereof and a sterile vehicle. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose, utilising a compound of the invention or pharmaceutically acceptable derivatives thereof and a sterile vehicle, optionally with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising 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. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions,

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the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of formula (I) or pharmaceutically acceptable salts thereof may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds of formula (I) or pharmaceutically acceptable salts thereof may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the compounds of formula (I) or pharmaceutically acceptable salts thereof, may be formulated as solutions for administration via a suitable metered or unitary dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device. Thus compounds of formula (I) or pharmaceutically acceptable salts thereof may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal



administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

5 The compounds of formula (I) or pharmaceutically acceptable salts thereof may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

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The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 15 0.05 to 1000 mg, 1.0 to 500mg or 1.0 to 200 mg and such unit doses may be administered more than once a day, for example two or three times a day.

20 Compounds of formula (I) or pharmaceutically acceptable salts thereof may be used in combination preparations. For example, the compounds of the invention may be used in combination with cyclosporin A, methotrexate, steroids, rapamycin, proinflammatory cytokine inhibitors, immunomodulators including biologicals or other therapeutically active compounds.

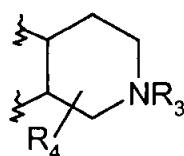
25 The subject invention also includes isotopically-labeled compounds, which are identical to those recited in formulas I and following, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of 30 hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, iodine, and chlorine, such as ^3H , ^{11}C , ^{14}C , ^{18}F , ^{123}I and ^{125}I .

Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labeled compounds 35 of the present invention, for example those into which radioactive isotopes such as ^3H , ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution

assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^8F isotopes are particularly useful in PET (positron emission tomography), and ^{125}I isotopes are particularly useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of formula (I) and following of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labelled reagent for a non-isotopically labeled reagent.

In a further aspect, this invention provides processes for the preparation of a compound of formula (I).

Compounds of formula (I) wherein B is

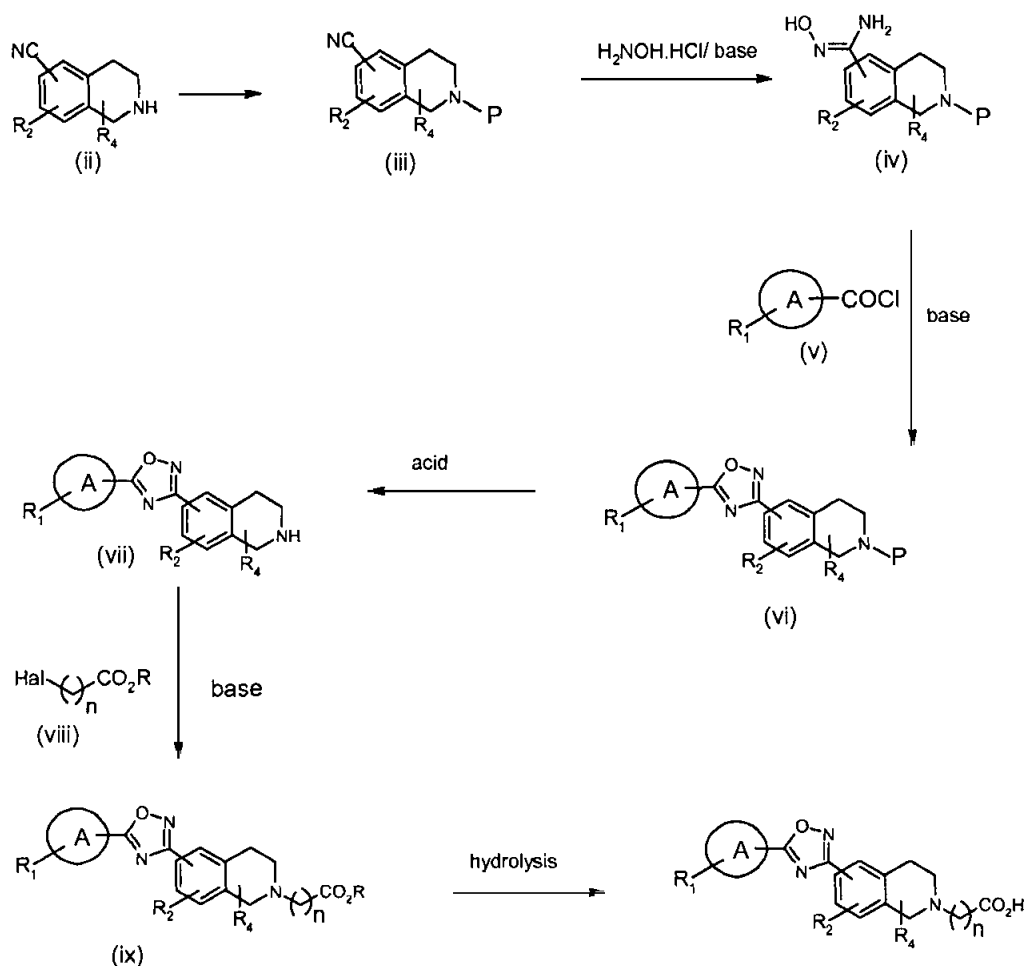


(a)

and R_3 is $(\text{CH}_2)_{1-3}\text{CO}_2\text{H}$ may be prepared according to Scheme 1, wherein R_1 , R_2 , R_4 and A are as defined for formula (I), n is 3, hal is chloro, bromo or iodo, P is a protecting group and R represents an alkyl group (eg ethyl or tert-butyl).

Scheme 1

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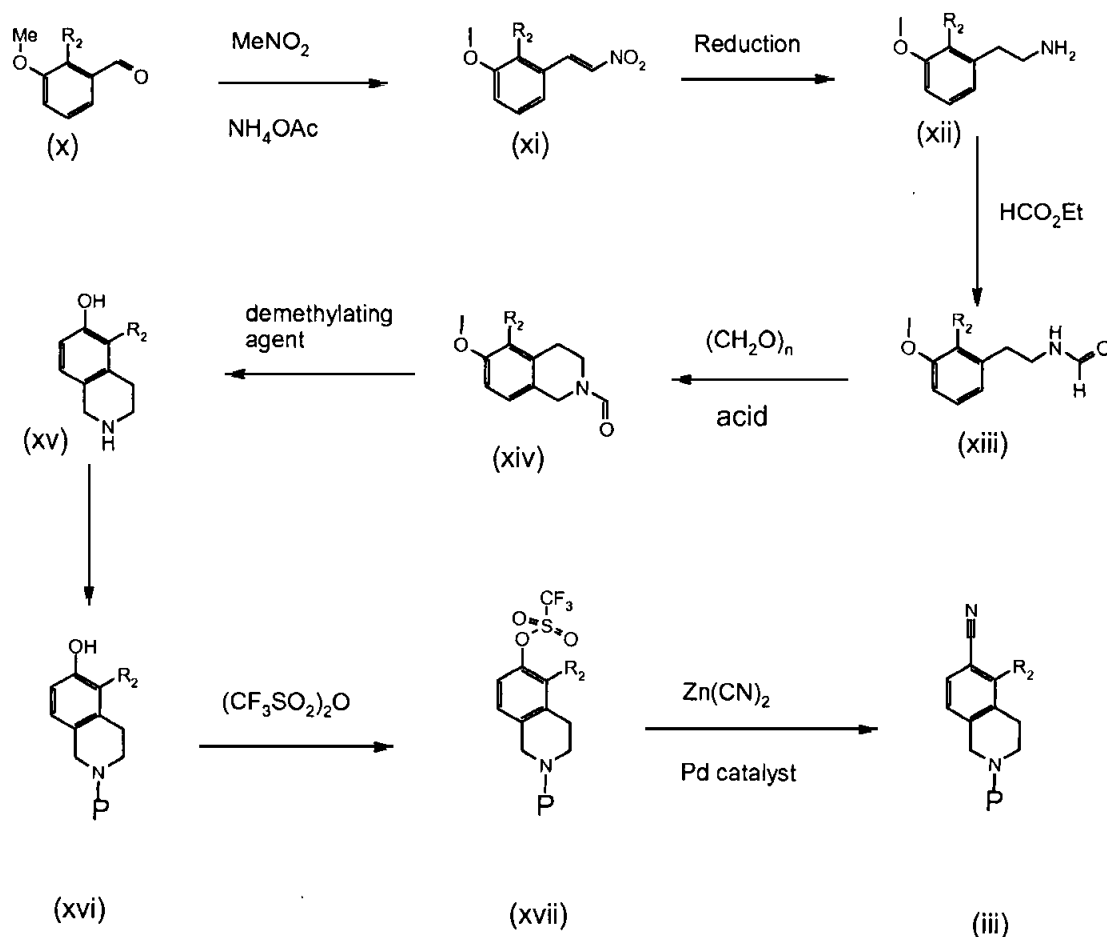
- Compounds of formula (ii) (for example prepared as described in Tetrahedron (2006), 62(29), 6869-6875) may be converted to a suitable protected derivative (iii),
- 5 where P is for example t-butoxycarbonyl, using a suitable protecting reagent such as bis(1,1-dimethylethyl) dicarbonate. Compounds of formula (iii) may be converted to compounds of formula (iv) by reaction with hydroxylamine in the presence of a suitable base such as sodium bicarbonate. Compounds of formula (iv) may be converted to compounds of formula (vi) by reaction with an acid chloride of formula
- 10 (v) in the presence of a suitable base such as *N,N*-diisopropylethylamine, optionally in the presence of a catalyst such as 4-dimethylaminopyridine. The reaction may be carried out at room temperature initially followed by heating to effect cyclisation to the oxadiazole. Compounds of formula (vi) may be deprotected to give compounds of formula (vii), for example with a suitable acid such as hydrochloric acid where P represents t-butoxycarbonyl. Compounds of formula (vii) may be converted into
- 15 compounds of formula (ix) by reaction with an alkylating agent of formula (viii) in the presence of a suitable base such as caesium carbonate. Compounds of formula (ix) may be converted into certain compounds of formula (I) by hydrolysis with a suitable

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base such as lithium hydroxide or (for R = t-butyl) a suitable acid such as hydrochloric acid or trifluoroacetic acid. Compounds of formula (v) are either known compounds or may be prepared by conventional means from the corresponding acids, which are themselves either known compounds or may be prepared by conventional means.

Compounds of formula (iii) wherein R₂ is in the 5-position and the cyano group is in the 6-position of the tetrahydroisoquinoline ring system may be prepared as shown in Scheme 2, wherein R₁ is defined for formula (I), R₄ is hydrogen and P is a protecting group.

Scheme 2



Compounds of formula (x) may be converted to compounds of formula (xii) by reaction with nitromethane in the presence of a suitable base such as ammonium

- acetate. Compounds of formula (xi) may be converted to compounds of formula (xii) by reduction with a suitable reducing agent such as lithium borohydride in the presence of chlorotrimethylsilane. Compounds of formula (xii) may be converted to compounds of formula (xiii) by reaction with a suitable formylating agent such as ethyl formate. Compounds of formula (xiii) may be converted to compounds of formula (xiv) by reaction with a suitable formaldehyde source such as paraformaldehyde, in the presence of a suitable acid catalyst such as formic acid. Compounds of formula (xiv) may be converted to compounds of formula (xv) by reaction with a suitable demethylating agent such as boron tribromide.
- 10 Compounds of formula (xv) may be converted to suitable protected derivatives of formula (xvi) where P is for example t-butoxycarbonyl, using a suitable protecting reagent such as bis(1,1-dimethylethyl) dicarbonate. Compounds of formula (xvi) may be converted to compounds of formula (xvii) by reaction with a suitable trifluoromethanesulphonylating agent such as trifluoromethanesulphonic anhydride.
- 15 Compounds of formula (xvii) may be converted to compounds of formula (iii) (wherein R₂ is in the 5-position, R₄ is hydrogen and the cyano group is in the 6-position) by reaction with a suitable cyanide source such as zinc cyanide in the presence of a suitable catalyst such as tetrakis(triphenylphosphine)palladium (0).

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All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

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The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Abbreviations:

- 30 g – grams
mg – milligrams
ml – millilitres
ul – microlitres
MeCN – acetonitrile
35 MeOH – methanol
EtOH – ethanol

	Et ₂ O –	diethyl ether
	EtOAc –	ethyl acetate
	DCM –	dichloromethane
	DIAD –	diisopropyl azodicarboxylate
5	DIPEA –	<i>N,N</i> -diisopropylethylamine
	DMAP –	<i>N,N</i> -dimethyl-4-pyridinamine
	DME –	1,2-bis(methoxy)ethane
	DMF –	<i>N,N</i> -dimethylformamide
	DMSO –	dimethylsulphoxide
10	EDAC –	<i>N</i> -(3-Dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide hydrochloride
	EDC –	<i>N</i> -(3-Dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide hydrochloride
	EDCI –	<i>N</i> -(3-Dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide hydrochloride
	HOBt/HOBt –	Hydroxybenzotriazole
	IPA –	isopropylalcohol
15	NCS –	<i>N</i> -chlorosuccinimide
	PyBOP –	Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
	THF –	tetrahydrofuran
	dba –	dibenzylidene acetone
	RT –	room temperature
20	°C –	degrees Celsius
	M –	Molar
	H –	proton
	s –	singlet
	d –	doublet
25	t –	triplet
	q –	quartet
	MHz –	megahertz
	MeOD –	deuterated methanol
	LCMS –	Liquid Chromatography Mass Spectrometry
30	LC/MS –	Liquid Chromatography Mass Spectrometry
	MS –	mass spectrometry
	ES –	Electrospray
	MH ⁺ –	mass ion + H ⁺
	MDAP –	mass directed automated preparative liquid chromatography.
35	sat. –	saturated
	Boc –	<i>tert</i> -butyloxycarbonyl

SCX or SCX-3 - solid phase extraction (SPE) column with benzene sulfonic acid residues immobilised on the solid phase (eg. IST Isolute™ columns).

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General chemistry section

The methods described below are given for illustrative purposes, intermediates in the preparation of the examples may not necessarily have been prepared from the specific batches described.

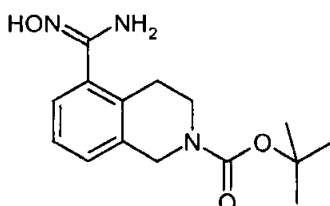
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Preparation 1

1,1-dimethylethyl

5-[(hydroxyamino)(imino)methyl]-3,4-dihydro-2(1H)-

isoquinolinecarboxylate



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1,2,3,4-tetrahydro-5-isoquinolinecarbonitrile hydrochloride (5.0 g/ 25.7 mmol, available from Fluorchem) was partitioned between DCM (100mL) and 2N NaOH. The DCM layer was collected, dried (hydrophobic frit) and evaporated. The free base, 1,2,3,4-tetrahydro-5-isoquinolinecarbonitrile was dissolved in dry DCM (100mL) and treated with bis(1,1-dimethylethyl) dicarbonate (1.1 equiv, 6.17g). The reaction was stirred at RT under argon for 18 h, washed with 2N NaOH (100mL), 2N HCl (100mL), dried (hydrophobic frit) and evaporated to give the crude 1,1-dimethylethyl-5-cyano-3,4-dihydro-2(1H)-isoquinolinecarboxylate which was used without further purification (LCMS 100%, NMR 2:1 mixture with tBuOH). Isolated yield 7.58 g. ¹H NMR (400 MHz, CDCl₃) δ (inter alia) 7.52 (1H, d), 7.35-7.16 (2H, m), 4.60 (2H, br.s), 3.71 (2H, t), 3.04 (2H, t), 1.5 (9H, s); m/z (API-ES) 203 [M+H-56]⁺.

25

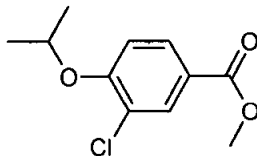
The crude material from above, hydroxylamine.HCl (14.31g, 206 mmol) and sodium bicarbonate (21.63g, 257 mmol) were added to a 500 mL round bottomed flask containing ethanol (200mL). The reaction mixture was heated at 65 °C for 24 hours. The cooled reaction was evaporated and partitioned between DCM (2x 100mL) and water (100mL). The combined DCM layers were collected and dried. Analysis by LC/MS showed the material to be ~80% pure. The material was dissolved in ethanol

30

(100mL) and filtered to remove undissolved impurities. Analysis by LC/MS showed the material to be ~92% pure. 1,1-dimethylethyl 5-[(hydroxyamino)(imino)methyl]-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate was used without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.82 (1H, br.s), 7.36-7.16 (3H, m), 4.80 (2H, br.s), 4.58 (2H, br.s), 3.59 (2H, br.t), 2.98 (2H, t), 1.49 (9H, s); m/z (API-ES) 292 [M+H]⁺.

Preparation 2

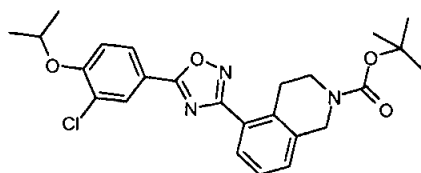
Methyl 3-chloro-4-[(1-methylethyl)oxy]benzoate



10 Methyl 3-chloro-4-hydroxybenzoate (50g, 0.27mole), K₂CO₃ (74g, 0.54mole) and iodopropane (29.5ml, 0.23mole) were stirred at room temperature in DMF (100mL). After 18 hours, the solvent was removed by evaporation under vacuum and the residue was chromatographed over a column of silica 60 in EtOAc/hexane (1:1) to give the title compound as an oil (55 g, 90%). ¹H NMR (400 MHz, CDCl₃) δ 8.05 (1H, d), 7.89 (1H, dd), 6.94 (1H, d), 4.60-4.72 (1H, m), 3.89 (3H, s), 1.41 (6H, d); m/z (API-ES) 229 [M+H]⁺.

Preparation 3

1,1-dimethylethyl 5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate

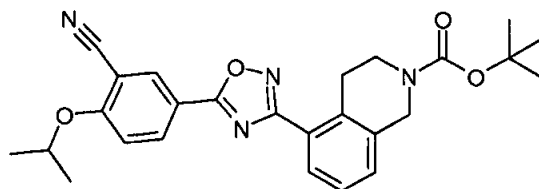


1,1-dimethylethyl 5-[(hydroxyamino)(imino)methyl]-3,4-dihydro-2(1*H*)-isoquinoline carboxylate (Preparation 1)(2 g, 6.86 mmol) was dissolved in tetrahydrofuran (THF) (100 mL) and stirred with sodium hydride (60% dispersion, 0.302 g, 7.55 mmol) under argon at room temperature for 30 minutes. Then methyl 3-chloro-4-[(1-methylethyl)oxy]benzoate (Preparation 2)(2.355 g, 10.30 mmol) was added and the reaction heated at reflux temperature for 1.5 hours. The cooled reaction was evaporated and partitioned between DCM (100mL) and water (100mL). The water layer was washed with DCM (50mL) and the combined DCM layers dried (hydrophobic frit) and evaporated. The crude product was purified by

chromatography through a small silica pad, eluting with DCM to yield 1,1-dimethylethyl 5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1H)-isoquinoline carboxylate (2.57 g, 5.47 mmol, 80 % yield). ¹H NMR (400 MHz, CDCl₃) δ 8.23 (1H, s), 8.05 (1H, d), 7.95 (1H, d), 7.34 (1H, t), 7.27 (1H, d), 7.06 (1H, d), 4.76-4.63 (1H, m), 4.66 (2H, br.s), 3.67 (2H, br.t), 3.25 (2H, br.t), 1.51 (9H, s), 1.45 (6H, d); m/z (API-ES) 414, 416 [M+H-56]⁺.

Preparation 4

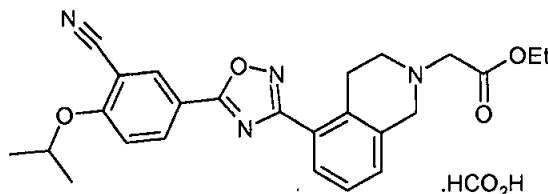
1,1-dimethylethyl 5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1H)-isoquinolinecarboxylate



To a solution of 3-cyano-4-[(1-methylethyl)oxy]benzoic acid (can be prepared as described in WO2005/58848, 737 mg, 3.59 mmol) and oxalyl chloride (360 μl) in DCM (20 mL) was added DMF (20 μl). The solution was stirred at room temperature for 90 min, then concentrated *in vacuo*, and redissolved in dry DMF (6 mL). Separately, 1,1-dimethylethyl 5-[(hydroxyamino)(imino)methyl]-3,4-dihydro-2(1H)-isoquinolinecarboxylate (Preparation 1, 1.05 g, 3.60 mmol), *N,N*-dimethyl-4-pyridinamine (DMAP) (20 mg) and *N,N*-diisopropylethylamine (DIPEA) (1.31 ml, 7.50 mmol) were dissolved in DMF (10 mL). 5 mL of the first DMF solution was added to the second solution, and the yellow solution stirred at room temperature for 1 h and then at 95 °C for 18 h. The reaction was concentrated *in vacuo* then partitioned between DCM (50 mL) and saturated aqueous NaHCO₃ (50 mL). The organics were washed with saturated aqueous NaHCO₃ (50 mL), then the combined aqueous extracted with DCM (20 mL). The combined organics were concentrated *in vacuo* to give a crude brown oil. Flash chromatography (gradient [0.5-4%] MeOH in DCM) and concentration *in vacuo* gave the title compound as a pale yellow solid (512 mg, 37%). ¹H NMR (400 MHz, CDCl₃) δ 8.42 (1H, d), 8.34 (1H, dd), 7.96 (1H, d), 7.34 (1H, t), 7.29 (1H, d), 7.13 (1H, d), 4.80 (1H, sept), 4.67 (2H, s), 3.68 (2H, t), 3.24 (2H, t), 1.51 (9H, s), 1.48 (6H, d); m/z (ES) 361 [M+H-100]⁺.

Preparation 5

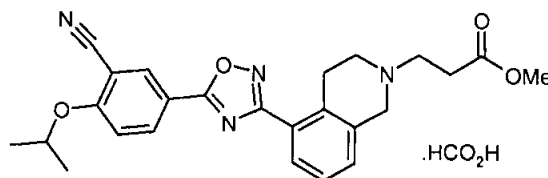
Ethyl [5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1H)-isoquinolinyl]acetate formic acid salt



A suspension of 2-[(1-methylethyl)oxy]-5-[3-(1,2,3,4-tetrahydro-5-isoquinolinyl)-1,2,4-oxadiazol-5-yl]benzonitrile (Example 3, 28.8 mg, 0.080 mmol), ethyl bromoacetate (35.5 μ l, 0.32 mmol) and Cs_2CO_3 (130 mg, 0.40 mmol) in DMF (2 mL) was stirred at room temperature for 1 h, and then irradiated to 60 $^\circ\text{C}$ for 5 min in the microwave. The suspension was added to an SCX cartridge, and the product eluted with methanolic ammonia. Concentration *in vacuo* gave a crude product (43 mg) that was purified by MDAP to give the title compound as a clear film (11.6 mg, 32 %). ^1H NMR (400 MHz, CDCl_3) δ 8.41 (1H, d), 8.33 (1H, dd), 8.09 (1H, br. s), 8.01 (1H, d), 7.34 (1H, apparent t), 7.21 (1H, d), 7.12 (1H, d), 4.80 (1H, sept), 4.24 (2H, q), 4.00 (2H, s), 3.52 (2H, s), 3.35 (2H, t), 3.07 (2H, t), 1.48 (6H, d), 1.31 (3H, t); m/z (ES) 447 $[\text{M}+\text{H}]^+$.

Preparation 6

Methyl 3-[5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1H)-isoquinolinyl]propanoate formic acid salt

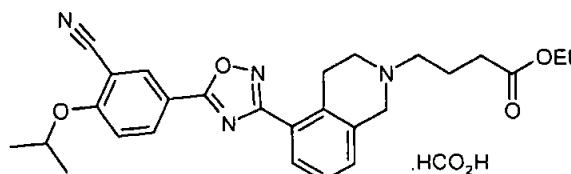


A suspension of 2-[(1-methylethyl)oxy]-5-[3-(1,2,3,4-tetrahydro-5-isoquinolinyl)-1,2,4-oxadiazol-5-yl]benzonitrile (Example 3, 28.8 mg, 0.080 mmol), methyl 3-bromopropionate (35 μ l, 0.32 mmol) and Cs_2CO_3 (130 mg, 0.40 mmol) in DMF (2 mL) was stirred at room temperature for 1 h, and then irradiated to 60 $^\circ\text{C}$ for 5 min in the microwave. More methyl 3-bromopropionate (35 μ l, 0.32 mmol) was added and the suspension was stirred at room temperature for 3.5 h, and then irradiated to increasing temperatures in the microwave until 150 $^\circ\text{C}$ for 30 min was achieved. The suspension was filtered and concentrated *in vacuo* then purified by MDAP to give the title compound as a yellow film (5.9 mg, 17 %). ^1H NMR (400 MHz, CDCl_3) δ 8.42 (1H, d), 8.33 (1H, dd), 8.21 (1H, br. s), 8.04 (1H, d), 7.35 (1H, t), 7.24 (1H, d), 7.13

(1H, d), 4.80 (1H, sept), 3.99 (2H, s), 3.72 (3H, s), 3.38 (2H, t), 3.12-3.06 (4H, m), 2.78 (2H, t), 1.48 (6H, d); m/z (ES) 447 [M+H]⁺.

Preparation 7

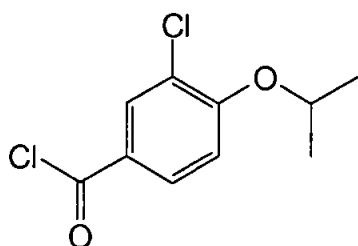
- 5 ethyl 4-[5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1H)-isoquinoliny]butanoate formic acid salt



- A suspension of 2-[(1-methylethyl)oxy]-5-[3-(1,2,3,4-tetrahydro-5-isoquinoliny)-1,2,4-oxadiazol-5-yl]benzonitrile (Example 3, 28.8 mg, 0.080 mmol), ethyl 4-bromobutyrate (45.8 μ l, 0.32 mmol) and Cs₂CO₃ (130 mg, 0.40 mmol) in DMF (2 mL) was stirred at room temperature for 1 h, and then irradiated to 60 °C for 5 min in the microwave. More ethyl 4-bromobutyrate (45.8 μ l, 0.32 mmol) was added and the suspension was stirred at room temperature for 3.5 h. It was then filtered, concentrated *in vacuo* and purified by MDAP to give the title compound as a yellow film (8.0 mg, 21 %). ¹H NMR (400 MHz, CDCl₃) δ 8.42 (1H, d), 8.34 (1H, dd), 8.27 (br. s), 8.09 (1H, d), 7.39 (1H, t), 7.27 (1H, d), 7.13 (1H, d), 4.80 (1H, sept), 4.19 (2H, s), 4.13 (2H, q), 3.47 (2H, t), 3.28 (2H, t), 2.99 (2H, t), 2.44 (2H, t), 2.10 (2H, quin), 1.48 (6H, d), 1.25 (3H, t); m/z (ES) 475 [M+H]⁺.

Preparation 8

3-Chloro-4-[(1-methylethyl)oxy]benzoyl chloride

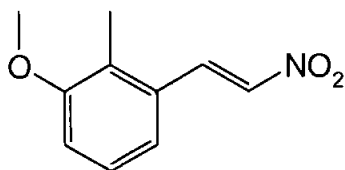


- A round bottom flask was charged with 3-chloro-4-[(1-methylethyl)oxy]benzoic acid (available from Paragos Product List, 10.2 g, 47.5 mmol), dichloromethane (158 ml) and oxalyl chloride (8.29 ml, 95 mmol). The reaction mixture was cooled to 0°C in an ice/water bath prior to the addition of *N,N*-dimethylformamide (0.158 ml). The solution was allowed to warm to ambient temperature overnight. The solvent was evaporated to yield the title compound as a cream solid (11.4g).

¹H NMR (CHLOROFORM-d) δ: 8.14 (d, 1H), 8.00 (dd, 2.5 Hz, 1H), 6.98 (d, 1H), 4.73 (spt, 1H), 1.44 (d, 6H)

Preparation 9

5 2-Methyl-1-(methyloxy)-3-[(E)-2-nitroethenyl]benzene



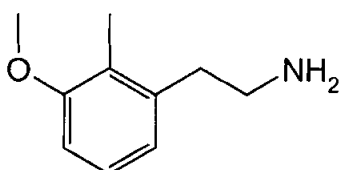
To a solution of 2-methyl-3-(methyloxy)benzaldehyde (available from Allichem Product List; 20g; 133 mmol) in nitromethane (400ml) was added ammonium acetate (6.16g; 80 mmol) and the resulting orange mixture was stirred for 1 h at 100°C then
10 cooled to room temperature and concentrated *in vacuo*. The residue was partitioned between ethyl acetate (x2) and brine, and the organic layers washed with brine, dried (MgSO₄) and concentrated *in vacuo*. Trituration with dichloromethane/ ether gave the title compound as a yellow solid (6.6g).

¹H NMR (CDCl₃) δ: 8.35 (d, 1H), 7.48 (d, 1H), 7.22 (t, 1H), 7.11 (d, 1H), 6.96 (d, 1H),
15 3.86 (s, 3H), 2.33 (s, 3H)

After evaporation of the mother liquors further product (7.22g) was obtained by trituration with diethyl ether. The mother liquors were again evaporated, and the residue was purified by chromatography, eluting with 5-10% ethyl acetate in
20 cyclohexane, to give further product (3.45g) after trituration with ether.

Preparation 10

{2-[2-Methyl-3-(methyloxy)phenyl]ethyl}amine



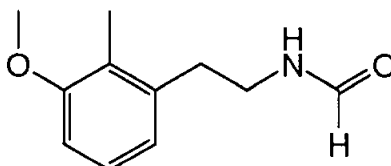
25 To lithium borohydride (2M in THF; 2.0ml; 4.0mmol) (cloudy) at room temperature was added dropwise over 0.5min chlorotrimethylsilane (1.02ml; 8.00 mmol). A precipitate was formed and after ca. 3 min, 2-methyl-1-(methyloxy)-3-[(E)-2-nitroethenyl]benzene (Preparation 9, 193 mg; 1.0mmol) in THF (4ml) was added dropwise via syringe over 5 min, making sure that the temperature remained at ca.

25°C (using a water cold bath). The solution was stirred at room temperature overnight. The mixture was cooled with an ice bath, methanol was added slowly, and the solvent removed *in vacuo*. The residue was partitioned between 25% aqueous sodium hydroxide and dichloromethane. The aqueous phase was separated and
5 extracted three times with dichloromethane and the combined organic layers evaporated. Purification of the residue by solid phase extraction (SCX column), eluting with methanol followed by 2N ammonia in methanol, followed by evaporation of the ammonia containing fraction gave the title compound (80mg).

¹H NMR (CDCl₃) δ: 7.10 (t, 1H), 6.78 (d, 1H), 6.73 (d, 1H), 3.81 (s, 3H), 2.91 (t, 2H),
10 2.77 (t, 2H), 2.18 (s, 3H), 1.76 (br. s., 2H)

Preparation 11

{2-[2-Methyl-3-(methyloxy)phenyl]ethyl}formamide

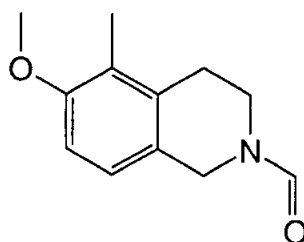


15 {2-[2-Methyl-3-(methyloxy)phenyl]ethyl}amine (Preparation 10; 1.75 g; 10.6 mmol) was heated under reflux with ethyl formate (97%; 15ml) for 15h. Removal of the solvent gave the crude product (ca. 2 g), which was purified by chromatography on silica gel, eluting with a gradient of 13-63% ethyl acetate in cyclohexane, to give the title compound (1.57g).

20 MS *m/z* 194 [MH⁺]

Preparation 12

5-Methyl-6-(methyloxy)-3,4-dihydro-2(1H)-isoquinolinecarbaldehyde



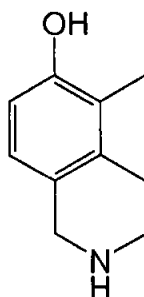
25 To a solution of {2-[2-methyl-3-(methyloxy)phenyl]ethyl}formamide (Preparation 11; 1.93g; 10.0 mmol) in formic acid (20ml) was added paraformaldehyde (0.315 g; 10.5 mmol) and the resulting mixture was heated under reflux (100°C) for 20min.

The mixture was cooled quickly to room temperature with ice cold water, and the solvent removed. Purification by chromatography on silica gel, eluting with a gradient of methanol in dichloromethane, gave the title compound as a white solid (1.64g), which was used without further purification.

5 MS m/z 206 $[MH^+]$

Preparation 13

5-Methyl-1,2,3,4-tetrahydro-6-isoquinolinol



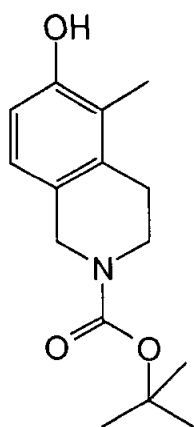
- 10 To a solution of 5-methyl-6-(methoxy)-3,4-dihydro-2(1H)-isoquinolinecarbaldehyde (Preparation 12; 1.49 g; 7.26 mmol) in dichloromethane (25ml) at 0°C under nitrogen was slowly added boron tribromide (9.09g; 36.3mmol). After 85min at 0°C, methanol (25 ml) was added slowly, and the resulting mixture was left standing at room temperature for three days. Removal of the solvent and trituration with methanol/
15 dichloromethane gave a white solid residue; the mother liquors were concentrated and the residue applied to an SCX solid phase extraction cartridge (20g) and eluted with methanol followed by 2N ammonia in methanol to elute the product. After evaporation of the solvent the title compound (780mg) was obtained as a pale yellow solid.
- 20 ^1H NMR (DMSO- d_6) δ : 8.91 (br. s., 1H), 6.62 (d, 1H), 6.56 (d, 1H), 3.70 (s, 2H), 2.92 (t, 2H), 2.48 (t, 2H), 1.96 (s, 3H)

Preparation 14

1,1-Dimethylethyl

6-hydroxy-5-methyl-3,4-dihydro-2(1H)-

25 **isoquinolinecarboxylate**

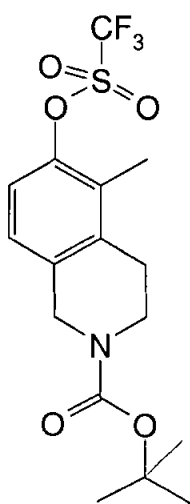


To a suspension of 5-methyl-1,2,3,4-tetrahydro-6-isoquinolinol (Preparation 13; 163 mg; 1.0mmol) in dichloromethane (5ml) at 0°C was added triethylamine (0.21 ml; 1.50 mmol) followed by bis(1,1-dimethylethyl) dicarbonate (240 mg; 1.10mmol).

- 5 The solvent was evaporated and the residue partitioned between ethyl acetate and brine. The aqueous layer was further extracted with ethyl acetate and the combined organic layers were dried (MgSO₄) and evaporated to give a yellow oil. Purification by flash chromatography eluting with a gradient of 5-25% ethyl acetate in cyclohexane gave the title compound as a white foam (232mg).
- 10 MS *m/z* 262 [M-H]

Preparation 15

1,1-Dimethylethyl 5-methyl-6-[[[(trifluoromethyl)sulfonyl]oxy]-3,4-dihydro-2(1H)-isoquinolinecarboxylate



15

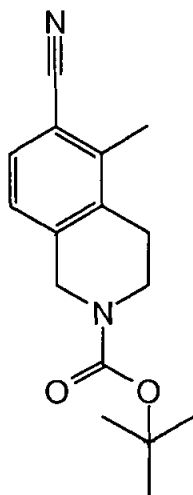
To a solution of 1,1-dimethylethyl 6-hydroxy-5-methyl-3,4-dihydro-2(1H)-isoquinolinecarboxylate (preparation 14; 263 mg; 1.00mmol) in dichloromethane (5ml) at -30°C under nitrogen was added pyridine (0.162 ml; 2.00mmol) followed by slow addition of trifluoromethanesulphonic anhydride (0.186ml; 1.10 mmol). After

0.5h between -30°C and -20°C, the solvent was removed, and the residue taken up in ethyl acetate. The solution was washed with 1N hydrochloric acid followed by saturated sodium bicarbonate solution, dried (MgSO₄) and concentration *in vacuo* to give the title compound as a pale yellow oil (368mg).

5 MS *m/z* 394 [M-H]

Preparation 16

1,1-Dimethylethyl 6-cyano-5-methyl-3,4-dihydro-2(1H)-isoquinolinecarboxylate



10

A solution of 1,1-dimethylethyl 5-methyl-6-(((trifluoromethyl)sulfonyl)oxy)-3,4-dihydro-2(1H)-isoquinolinecarboxylate (Preparation 15; 395mg; 1.00mmol) in DMF (4ml) was de-gassed under high vacuum with stirring for 15 min, followed by addition of zinc cyanide (153mg; 1.30mmol) and tetrakis(triphenylphosphine)palladium (0) (116mg; 0.10mmol) under nitrogen. The resulting deep yellow mixture was stirred at 100°C for 6 h. The solvent was removed, the residue dissolved in ethyl acetate, and the solution washed with saturated sodium bicarbonate. The aqueous layer was further extracted with ethyl acetate, and the combined organic layers washed with brine, dried (MgSO₄), and evaporated to give the crude product. Purification by flash chromatography on silica gel, eluting with a gradient of 5-25% ethyl acetate in cyclohexane, gave the title compound (214 mg) as a white solid.

15

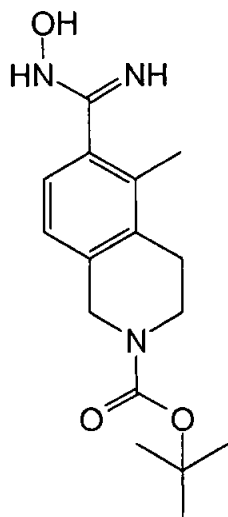
20

¹H NMR (CDCl₃) δ: 7.44 (d, 1H), 7.04 (d, 1H), 4.60 (s, 2H), 3.69 (t, 2H), 2.75 (t, 2H), 2.46 (s, 3H), 1.49 (s, 9H)

25

Preparation 17

1,1-Dimethylethyl 6-[(hydroxyamino)(imino)methyl]-5-methyl-3,4-dihydro-2(1H)-isoquinolinecarboxylate



1,1-Dimethylethyl 6-cyano-5-methyl-3,4-dihydro-2(1H)-isoquinolinecarboxylate

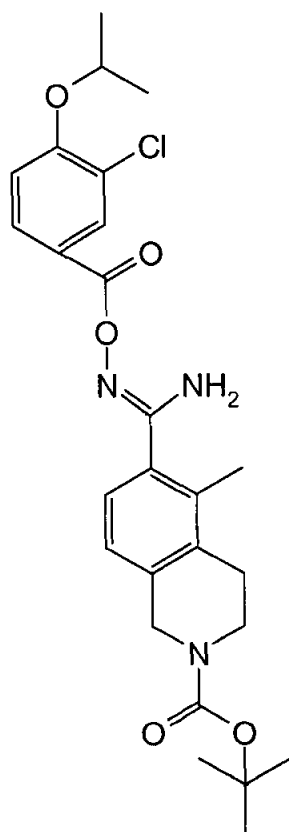
- 5 (Preparation 16; 404mg; 1.48mmol) was stirred overnight at 80°C with hydroxylamine hydrochloride (619mg; 8.90mmol) and sodium bicarbonate (748mg; 8.9mmol) in ethanol (10ml). Further sodium bicarbonate (400 mg) and hydroxylamine hydrochloride (300 mg) were added, and heating continued for ca. 8h. The mixture was cooled to room temperature, and the resulting solid removed,
10 washed with ethanol, and dried under high vacuum to give the title compound as a white solid (431mg).

¹H NMR (DMSO-d₆) δ: 7.06 (d, 1H), 6.99 (d, 1H), 4.48 (br. s., 2H), 3.58 (t, 2H), 2.67 (t, 2H), 2.19 (s, 3H), 1.42 (s, 9H) (exchangeables not listed; not clearly observed).

15 **Preparation 18**

1,1-Dimethylethyl

6-[[[[(3-chloro-4-[(1-methylethyl)oxy]phenyl)carbonyl)oxy]amino](imino)methyl]-5-methyl-3,4-dihydro-2(1H)-isoquinolinecarboxylate

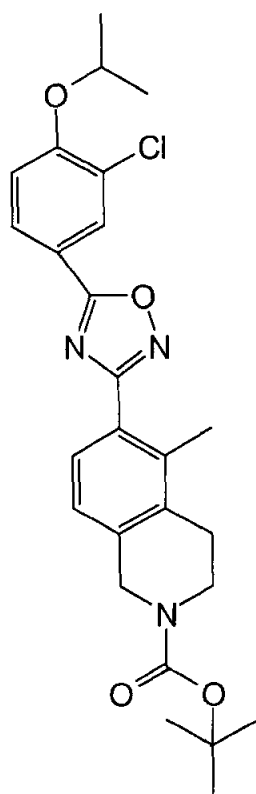


To a solution of 1,1-dimethylethyl 6-[(hydroxyamino)(imino)methyl]-5-methyl-3,4-dihydro-2(1H)-isoquinolinecarboxylate (Preparation 17; 435mg; 1.42mmol) in dichloromethane (10 ml) was added triethylamine (0.30 ml; 2.14 mmol) followed by
5 3-chloro-4-[(1-methylethyl)oxy]benzoyl chloride (Preparation 8; 365mg; 1.57mmol) in dichloromethane (5 ml). After 30 min, the reaction was concentrated, and the residue partitioned between ethyl acetate and saturated sodium bicarbonate. The aqueous layer was further extracted with ethyl acetate, and the combined organic layers washed with brine, dried (MgSO₄) and concentrated *in vacuo*. Purification by flash
10 chromatography on silica gel, eluting with a gradient of 10-50% ethyl acetate in cyclohexane gave the title compound as a white foam (413 mg).

MS *m/z* 500 [M-H]

Preparation 19

15 **1,1-Dimethylethyl 6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinolinecarboxylate**

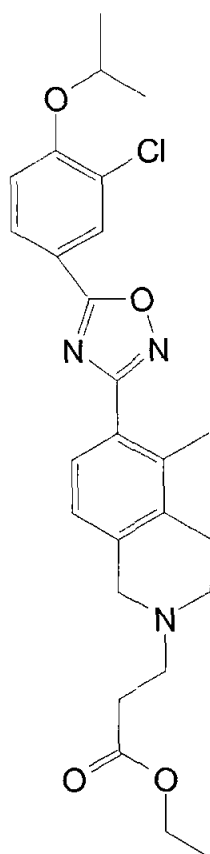


A solution of 1,1-dimethylethyl 6-[[[3-chloro-4-[(1-methylethyl)oxy]phenyl]carbonyl]oxy]amino}{(imino)methyl]-5-methyl-3,4-dihydro-2(1H)-isoquinolinecarboxylate (Preparation 18; 413mg; 0.823mmol) in 1,4-dioxane(15 ml) was stirred at 110°C for ca. 18h. The mixture was cooled to room temperature and the solvent removed. Purification by flash chromatography on silica gel, eluting with 5-25% ethyl acetate in cyclohexane followed by 13-63% ethyl acetate in cyclohexane, gave the title compound as a white foam (220mg).

¹H NMR (CHLOROFORM-d) δ: 8.24 (d, 1H), 8.05 (dd, 1H), 7.76 (d, 1H), 7.10 (d, 1H), 7.06 (d, 1H), 4.72 (spt, 1H), 4.63 (s, 2H), 3.71 (t, 2H), 2.84 (t, 2H), 2.52 (s, 3H), 1.51 (s, 9H), 1.45 (d, 6H)

Preparation 20

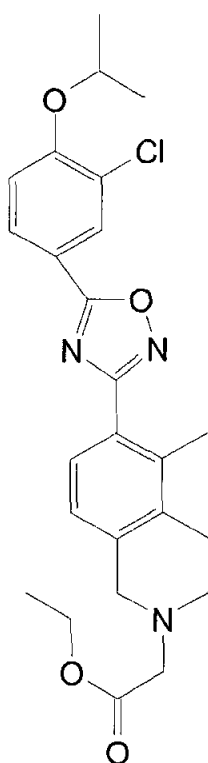
Ethyl 3-[6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinolinyl]propanoate



To a suspension of 6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-1,2,3,4-tetrahydroisoquinoline trifluoroacetate (Example 10; 90mg; 0.18mmol) in acetonitrile (3ml) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 0.16ml; 1.09mmol). Ethyl acrylate (0.03ml; 0.27mmol) was added to the solution and the resulting mixture stirred at 70°C for 0.5h. The mixture was cooled to room temperature and the solvent removed. The residue was partitioned between ethyl acetate and brine, and the aqueous layer further extracted with ethyl acetate. The combined organic layers were washed with brine, dried (MgSO₄) and concentrated *in vacuo* to give the title compound (90mg).
MS *m/z* 484 [MH⁺]

Preparation 21

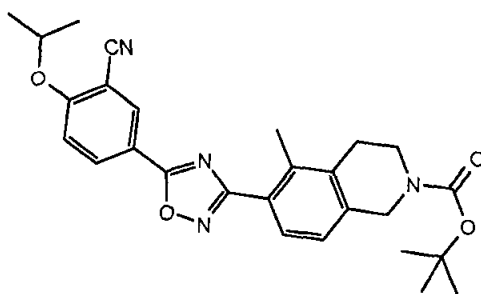
Ethyl [6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinolinyl]acetate



- To a suspension of 6-(5-(3-chloro-4-((1-methylethyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)-5-methyl-1,2,3,4-tetrahydroisoquinoline trifluoroacetate (Example 10; 90mg; 0.18mmol) in DMF (3ml) under nitrogen at room temperature was added caesium carbonate (177mg; 0.54mmol) followed by ethyl bromoacetate (0.026ml; 0.23mmol). After 35min, the mixture was diluted with ethyl acetate and the precipitate removed. The solution was washed with water and the aqueous layer further extracted with ethyl acetate. The organic layer was washed with brine, dried over MgSO_4 and concentrated *in vacuo* to give the title compound (75mg).
- MS m/z 470 $[\text{MH}^+]$

Preparation 22

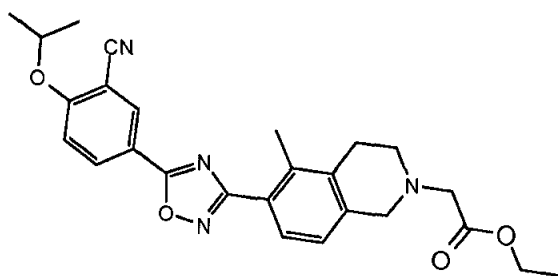
1,1-Dimethylethyl 6-(5-(3-cyano-4-((1-methylethyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinolinecarboxylate



- Oxalyl chloride (571mg, 4.5mmol) was added to a solution of 3-cyano-4-[(1-methylethyl)oxy]benzoic acid (available from AK Scientific Product Catalog; 800mg, 3.90mmol) in dichloromethane (15ml) followed by DMF (catalytic amount).
- 5 The reaction mixture was stirred for 45 minutes, further oxalyl chloride (0.1ml) and DMF (1drop) were added and stirring continued for 20 minutes. The solvent was evaporated, the residue was co-evaporated with toluene then dried under high vacuum for 30 minutes. The crude acid chloride was dissolved in acetonitrile (10ml) and added to a suspension of 1,1-dimethylethyl 6-[(hydroxyamino)(imino)methyl]-5-methyl-3,4-dihydro-2(1H)-isoquinolinecarboxylate (Preparation 17; 916mg, 3.00
- 10 mmol) and triethylamine (607mg, 6.00mmol) in acetonitrile (15ml). The reaction mixture was stirred at room temperature for 40 minutes then heated under reflux for 24 hours. The reaction mixture was cooled and the solvent evaporated. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution.
- 15 The organic phase was separated, washed with brine, dried (MgSO₄) and evaporated to give the crude product (1.3g). The residue was purified by chromatography, eluting with 8-38% ethyl acetate in cyclohexane, to give the title compound (486mg).
- ¹H NMR (CHLOROFORM-d) δ: 8.42 (d, 1H), 8.33 (dd, 1H), 7.76 (d, 1H), 7.12 (d, 1H), 7.11 (d, 1H), 4.80 (spt, 1H), 4.64 (s, 2H), 3.72 (t, 2H), 2.84 (t, 2H), 2.52 (s, 3H), 1.51 (s, 9H), 1.48 (d, 6H)
- 20

Preparation 23

- Ethyl [6-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinolinyl]acetate
- 25



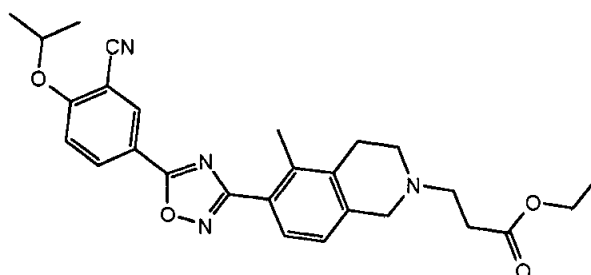
- A mixture of 2-[(1-methylethyl)oxy]-5-[3-(5-methyl-1,2,3,4-tetrahydro-6-isoquinolinyl)-1,2,4-oxadiazol-5-yl]benzonitrile trifluoroacetic acid salt (Example 11; 100mg, 0.20mmol), ethyl bromoacetate (44mg, 30μl, 0.26mmol) and caesium carbonate
- 30

(200mg, 0.61mmol) in dry DMF (3ml) was stirred at room temperature for 1 hour. The reaction mixture was diluted with water (10ml) and extracted with ethyl acetate (3x5ml). The combined extracts were dried and evaporated. Purification by chromatography on silica gel, eluting with 10% ethyl acetate in cyclohexane gave the
5 title compound as a colourless oil (85mg). MS m/z 461 $[MH]^+$.

Preparation 24

Ethyl 3-[6-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinolinyl]propanoate

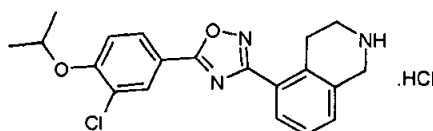
10



A mixture of 2-[(1-methylethyl)oxy]-5-[3-(5-methyl-1,2,3,4-tetrahydro-6-isoquinolinyl)-1,2,4-oxadiazol-5-yl]benzonitrile trifluoroacetic acid salt (Example 11; 100mg,
15 0.20mmol), ethyl acrylate (31mg, 33 μ l, 0.31mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 187mg, 185 μ l, 1.23mmol) in acetonitrile (3ml) was stirred at room temperature for 3 hours. The solvent was evaporated and the residue dissolved in ethyl acetate (10ml); the solution was washed with water (5ml), dried and evaporated. Purification of the residue by chromatography on silica gel, eluting with
20 10% ethyl acetate in cyclohexane gave the title compound as a colourless oil (86mg). MS m/z 475 $[MH]^+$.

Example 1

5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,3,4-tetrahydroisoquinoline hydrochloride
25

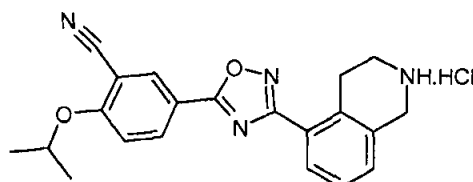


1,1-dimethylethyl 5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1H)-isoquinolinecarboxylate (Preparation 3) (2.57 g, 5.47 mmol) was stirred in 4M HCl in 1,4-Dioxane (100 mL). After 1 hour reaction became cloudy and

stirring continued for a further 16 hours. Evaporation yielded 5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (2.23 g, 5.49 mmol, 100 % yield). ¹H NMR (400 MHz, d₆-DMSO) δ 9.43 (2H, s), 8.19 (1H, s), 8.11 (1H dd), 8.03-8.00 (1H, m), 7.51-7.45 (3H, m), 4.89 (1H, sept.), 4.38 (2H, s), 3.43 (2H, t), 3.35-3.32 (2H, m), 1.37 (6H, d); m/z (API-ES) 370, 372 [M+H]⁺.

Example 2

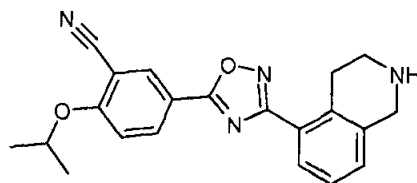
2-[(1-methylethyl)oxy]-5-[3-(1,2,3,4-tetrahydro-5-isoquinolinyl)-1,2,4-oxadiazol-5-yl]benzonitrile hydrochloride



A mixture of 1,1-dimethylethyl 5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (Preparation 4; 53.7 mg, 0.117 mmol) and 4M HCl in dioxane (2 ml) was stirred at room temperature for 64 h. The mixture was concentrated *in vacuo*, the residue triturated with Et₂O and dried *in vacuo* to leave a light brown solid (35.1 mg, 76 %). ¹H NMR (400 MHz, d₆-DMSO) δ 9.52 (2H, br. s), 8.52 (1H, d), 8.40 (1H, dd), 8.02 (1H, dd), 7.57, (1H, d), 7.51-7.48 (2H, m), 4.99 (1H, sept.), 4.38 (2H, s), 3.39-3.34 (4H, m), 1.39 (6H, d); m/z (ES) 361 [M+H]⁺.

Example 3

2-[(1-methylethyl)oxy]-5-[3-(1,2,3,4-tetrahydro-5-isoquinolinyl)-1,2,4-oxadiazol-5-yl]benzonitrile

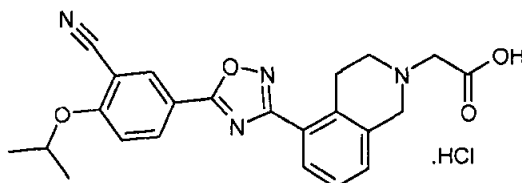


A mixture of 1,1-dimethylethyl 5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (Preparation 4, 512 mg, 1.11 mmol) and 4M HCl in dioxane (20 ml) was stirred at room temperature for 18 h. The mixture was concentrated *in vacuo* to give a pale yellow solid, which was

redissolved in MeOH. This solution was applied to an SCX-3 cartridge (10 g), and the product eluted with 1% NH₃ in MeOH. Concentration gave a yellow oil, that became a solid on standing overnight (366 mg, 91%). ¹H NMR (400 MHz, d₆-DMSO) δ 8.38 (1H, d), 8.32 (1H, dd), 7.94 (1H, d), 7.32-7.17 (2H, m), 7.13 (1H, m), 4.80 (1H, sept), 4.10 (2H, s), 3.20-3.14 (4H, m), 1.48 (6H, d); m/z (ES) 361 [M+H]⁺.

Example 4

[5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1H)-isoquinoliny]acetic acid hydrochloride



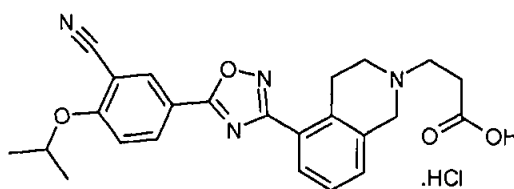
10

A solution of ethyl [5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1H)-isoquinoliny]acetate formic acid salt (Preparation 5, 11.6 mg, 0.026 mmol) and LiOH (0.3 mg) in THF-MeOH-water (300μl, 300μl, 200 μL) was irradiated to 100 °C for 3 min in the microwave. 2M aqueous HCl (1 mL) was added, then the solution extracted with DCM (2 x 2 mL). The combined organics were concentrated *in vacuo* to give the title compound as a white solid (10.1 mg, 85 %). ¹H NMR (400 MHz, d₄-MeOH) δ 8.48 (1H, d), 8.44 (1H, dd), 8.21 (1H, d), 7.44 (1H, t), 7.47 (2H, apparent d), 4.97 (1H, sept), 4.70 (2H, s), 4.32 (2H, s), 3.67 (2H, t), 3.57 (2H, t), 1.47 (6H, d); m/z (ES) 419 [M+H]⁺.

20

Example 5

3-[5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1H)-isoquinoliny]propanoic acid hydrochloride



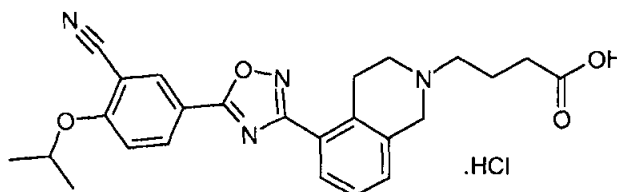
A solution of methyl 3-[5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1H)-isoquinoliny]propanoate formic acid salt (Preparation 6, 5.9 mg, 0.0132 mmol) and LiOH (0.15 mg) in THF-MeOH-water (300μl, 300μl, 100μl) was irradiated to 100 °C for 3 min in the microwave. 2M aqueous HCl (1 ml) and DCM (2 ml) were added sequentially, and a precipitate formed. Filtration gave the

title compound as a white solid (6.5 mg, quant.). ^1H NMR (400 MHz, $\text{d}_6\text{-DMSO}$) δ 12.71 (1H, br s), 11.41 (1H, br s), 8.53 (1H, d), 8.41 (1H, dd), 8.05 (1H, d), 7.57 (1H, d), 7.53 (1H, t), 7.46 (1H, d), 4.99 (1H, sept), 4.53 (2H, br s), 3.46-3.43 (4H, m), 3.65 (2H, br s), 2.98 (2H, t), 1.39 (6H, d); m/z (ES) 433 $[\text{M}+\text{H}]^+$.

5

Example 6

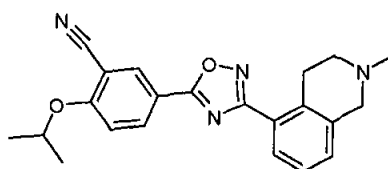
4-[5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1H)-isoquinoliny]butanoic acid hydrochloride



- 10 The title compound was made in similar fashion to Example 4, replacing ethyl [5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1H)-isoquinoliny]acetate with ethyl 4-[5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1H)-isoquinoliny]butanoate formic acid salt (Preparation 7, 8.0 mg). The title compound was obtained as a white solid (10.1 mg).
- 15 ^1H NMR (400 MHz, $\text{d}_4\text{-MeOH}$) δ 8.36 (1H, d), 8.33 (1H, dd), 8.23 (1H, d), 7.43 (1H, t), 7.37 (1H, d), 7.35 (1H, d), 4.85 (1H, sept), 4.52 (2H, br s), 3.63-3.54 (4H, br. m), 3.30 (2H, apparent dd), 2.43 (2H, t), 2.06 (2H, quin), 1.36 (6H, d); m/z (ES) 447 $[\text{M}+\text{H}]^+$.

Example 7

- 20 **2-[(1-methylethyl)oxy]-5-[3-(2-methyl-1,2,3,4-tetrahydro-5-isoquinoliny)-1,2,4-oxadiazol-5-yl]benzonitrile**

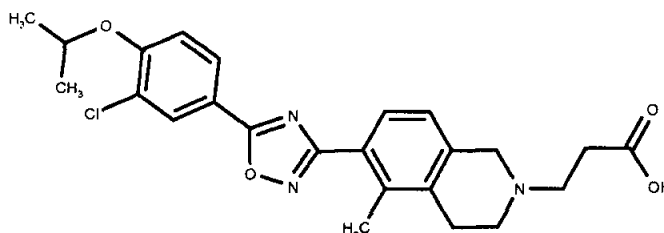


- To a solution of 2-[(1-methylethyl)oxy]-5-[3-(1,2,3,4-tetrahydro-5-isoquinoliny)-1,2,4-oxadiazol-5-yl]benzonitrile (Example 3, 25.0 mg, 0.069 mmol) and formaldehyde (37% w/v in H_2O , 8.0 μL , 0.10 mmol) in DCM (5 mL) was added $\text{NaBH}(\text{OAc})_3$ (29 mg, 0.14 mmol) and the resulting solution stirred at room temperature for 20 min. Brine (5 mL) was added, and the aqueous extracted with DCM (5 mL). The combined organics were concentrated *in vacuo* to give a white solid. This solid was redissolved in DMSO-MeOH, added to an SCX cartridge and washed with MeOH. The product
- 25
- 30 was eluted with NH_3 in MeOH; concentration *in vacuo* gave a white solid (20.1 mg,

78 %). ^1H NMR (400 MHz, CDCl_3) δ 8.41 (1H, d), 8.32 (1H, dd), 7.98 (1H, d), 7.29 (1H, t), 7.20 (1H, d), 7.12 (1H, d), 4.79 (1H, sept), 3.67 (2H, s), 3.30 (2H, t), 2.75 (2H, t), 2.49 (3H, s), 1.47 (6H, d).

5 **Example 8**

3-[6-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinolinyl]propanoic acid



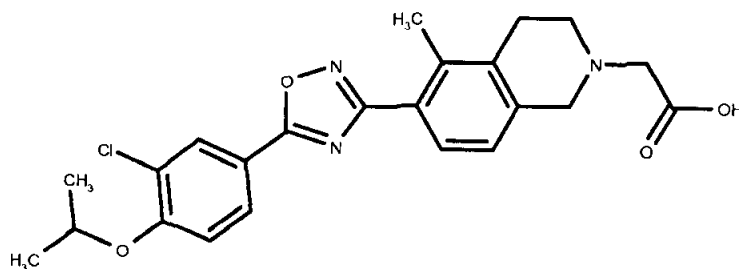
To a solution of ethyl 3-[6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinolinyl]propanoate (Preparation 20; 90mg; 0.186mmol) in ethanol (2ml) and THF (2ml) at room temperature was added 2N sodium hydroxide (0.186 ml; 0.372 mmol), and the resulting mixture was stirred at room temperature for ca. 2.5 h. Removal of most of the solvents, dilution with ca. 1 ml of water, followed by addition of acetic acid (ca. 300 μ l) gave a precipitate. The mixture was extracted with dichloromethane to give, after removal of the solvent and trituration with diethyl ether, the title compound as a white solid (40mg).

^1H NMR ($\text{DMSO}-d_6$) δ : 8.15 (d, 1H), 8.09 (dd, 1H), 7.64 (d, 1H), 7.43 (d, 1H), 7.09 (d, 1H), 4.88 (spt, 1H), 3.64 (s, 2H), 2.76 (br. s., 4H), 2.72 (t, 2H), 2.44 (t, 2H), 2.41 (s, 3H), 1.36 (d, 6H)

MS m/z 456 [MH^+]

Example 9

[6-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinolinyl]acetic acid



241

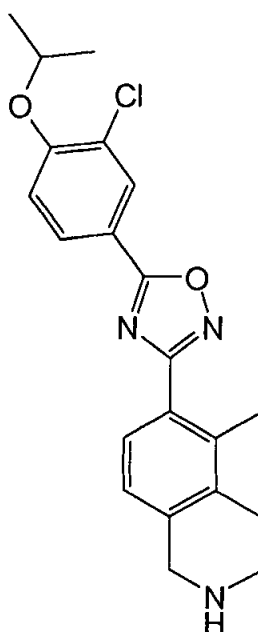
To a solution of ethyl [6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinoliny]acetate (Preparation 21; 75mg ; 0.16mmol) in ethanol (2ml) and THF (2ml) at room temperature was added 2N sodium hydroxide, and the resulting mixture was stirred at room temperature for 40min. The solvents were removed and the residue dissolved in water (ca. 1 ml). Acetic acid (1ml) was added, all solvents were removed and the residue co-evaporated with toluene to give a pale yellow solid. This solid was triturated with diethyl ether to give the title compound, which was filtered off as a pale yellow solid (50mg).

MS m/z 442 [MH^+]

^1H NMR (DMSO- d_6) δ : 8.16 (br. s., 1H), 8.10 (d, 1H), 7.62 (d, 1H), 7.44 (d, 1H), 7.05 (d, 1H), 4.88 (spt, 1H), 3.70 (br. s., 2H), 2.91 (br. s., 2H), 2.77 (br. s., 4H), 2.42 (br. s., 3H), 1.36 (d, 6H).

Example 10

6-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-1,2,3,4-tetrahydroisoquinoline trifluoroacetate



To a solution of 1,1-dimethylethyl 6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinolinecarboxylate (Preparation 19; 210mg; 0.434mmol) in dichloromethane (3ml) at 0°C was added trifluoroacetic acid (3ml) dropwise. The resulting mixture was stirred at 0°C for 1h, giving a pale yellow solution. Removal of the solvent and co-evaporation with toluene gave a white solid,

which was triturated with diethyl ether to give the title compound as a white solid (206 mg).

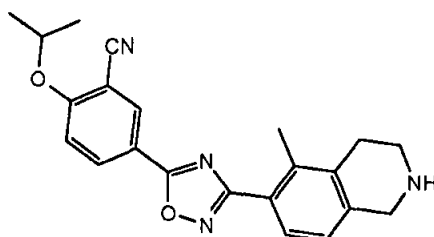
¹H NMR (DMSO-d₆) δ: 9.08 (br. s., 2H), 8.17 (d, 1H), 8.10 (dd, 1H), 7.78 (d, 1H), 7.45 (d, 1H), 7.28 (d, 1H), 4.84 - 4.94 (m, 1H), 4.38 (br. s., 2H), 3.45 - 3.52 (m, 2H), 2.98

5 (t, 2H), 2.46 (s, 3H), 1.36 (d, 6H)

MS *m/z* 384 [MH⁺]

Example 11

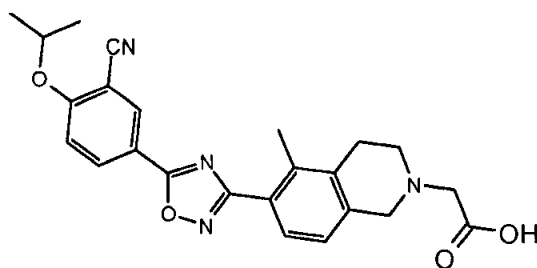
2-[(1-Methylethyl)oxy]-5-[3-(5-methyl-1,2,3,4-tetrahydro-6-isoquinolinyl)-1,2,4-oxadiazol-5-yl]benzonitrile trifluoroacetic acid salt



Trifluoroacetic acid (3ml) was added to an ice cooled solution of 1,1-dimethylethyl 6-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinolinecarboxylate (Preparation 22; 486mg, 1.02mmol) in dichloromethane (3ml). The reaction mixture was stirred at 0°C for 30 minutes. The solvent was evaporated and the residue co-evaporated from toluene (x2). Trituration of the residue with diethyl ether gave the title compound as a colourless solid which was filtered off and dried (485mg). ¹H NMR (400 MHz, CDCl₃) δ: 1.48 (6H, d), 2.54 (3H, s), 3.09 (2H, m), 3.5 (2H, obscured by residual solvent), 4.36 (2H, s), 4.80 (1H, m), 7.08-7.15 (2H, m), 7.85 (1H, d), 8.33 (1H, d), 8.42 (1H, s), 10.20 (2H, br s). MS *m/z* 375 [MH]⁺.

Example 12

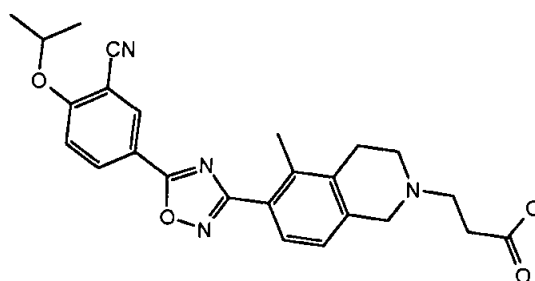
[6-(5-{3-Cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinolinyl]acetic acid



2M Sodium hydroxide (2ml) was added to a suspension of ethyl [6-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinolinyl]acetate (Preparation 23; 80mg, 0.17mmol) in ethanol (2ml). The reaction mixture was stirred at room temperature for 2 hours. The solvent was evaporated and the residue diluted with water (5ml). The solution was acidified with acetic acid and extracted with ethyl acetate (3x5ml). The aqueous phase was evaporated and the residue purified by MDAP to give the title compound as a colourless solid (7mg). ¹H NMR (400 MHz, d₄MeOH) δ: 1.46 (6H, d), 2.55 (3H, s), 3.19 (2H, t), 3.35 (2H, s), 3.67 (2H, t), 3.78 (2H, s), 4.53 (2H, s), 4.95 (1H, m) (part obscured by water peak), 7.20 (1H, d), 7.54 (1H, d), 7.85 (1H, d), 8.50-8.60 (2H, m). MS *m/z* 433 [MH]⁺.

Example 13

3-[6-(5-{3-Cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinolinyl]propanoic acid sodium salt



2M sodium hydroxide (2ml) was added to a solution of ethyl 3-[6-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinolinyl]propanoate (Preparation 24; 80mg, 0.17mmol) in ethanol (2ml) at 60°C. The reaction mixture was stirred at 60°C for 2 hours, cooled to room temperature and diluted with water (2ml). The solid was filtered off, washed with a small amount of water and dried to give the title compound as a colourless solid (55mg). ¹H NMR (400 MHz, d₆DMSO) δ: 1.39 (6H, d), 2.08 (2H, t), 2.44 (3H, s), 2.59-2.78 (6H, m),

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3.56 (2H, s), 4.98 (1H, m), 7.09 (1H, d), 7.55 (1H, d), 7.65 (1H, d), 8.40 (1H, dd), 8.50 (1H, s). MS m/z 447 [MH]⁺.

Membrane preparation for S1P1 GTP γ S assay

5 For membrane preparations all steps were performed at 4°C. Rat hepatoma cells stably expressing the human S1P1 receptor or Rat Basophilic Leukaemia cells (RBL) stably expressing human S1P3 receptor were grown to 80% confluency before being harvested into 10ml Phospho-Buffered Saline (PBS) and centrifuged at 1200rpm for 5 minutes. After removal of the supernatant, the pellet was re-suspended and cells
10 were homogenised within a glass Waring blender for 2 bursts of 15secs in 200mls of buffer (50mM HEPES, 1mM leupeptin, 25 μ g/ml bacitracin, 1mM EDTA, 1mM PMSF, 2 μ M pepstatin A). The blender was plunged into ice for 5 mins after the first burst and 10-40 mins after the final burst to allow foam to dissipate. The material was then spun at 500g for 20 mins and the supernatant spun for 36 mins at 48,000g. The
15 pellet was resuspended in the same buffer as above but without PMSF and pepstatin A. The material was then forced through a 0.6mm needle, made up to the required volume, (usually x4 the volume of the original cell pellet), aliquoted and stored frozen at -80°C.

20 Alternative Membrane preparation for S1P1 GTP γ S assay

All steps were performed at 4°C. Cells were homogenised within a glass Waring blender for 2 bursts of 15 secs in 200mls of buffer (50mM HEPES, 1mM leupeptin, 25 μ g/ml bacitracin, 1mM EDTA, 1mM PMSF, 2 μ M pepstatin A). The blender was plunged into ice for 5 mins after the first burst and 10-40 mins after the final burst to
25 allow foam to dissipate. The material was then spun at 500g for 20 mins and the supernatant spun for 36 mins at 48,000g. The pellet was resuspended in the same buffer as above but without PMSF and pepstatin A. The material was then forced through a 0.6mm needle, made up to the required volume, (usually x4 the volume of the original cell pellet), aliquoted and stored frozen at -80°C

30

S1P1 GTP γ S assay

Human S1P1 rat hepatoma membranes (1.5 μ g/well) were adhered to a wheatgerm agglutinin (WGA)-coated scintillation proximity assay (SPA) beads (0.125mg/well) in
35 assay buffer (HEPES 20mM, MgCl₂ 10mM, NaCl 100mM and pH adjusted to 7.4

using KOH 5M, GDP 10 μ M FAC (final assay concentration) and saponin 90 μ g/ml FAC was also added).

After 30 minutes pre-coupling on ice the bead and membrane suspension was dispensed into a white Greiner polypropylene LV384-well plate (5 μ l/well), containing
5 0.1 μ l of the compound. 5 μ l/well [³⁵S]-GTP γ S (0.5nM final radioligand conc) made up in assay buffer was then added to agonist plates. The final assay cocktail (10.1 μ l) was then centrifuged at 1000rpm for 5 minutes then read immediately on a Viewlux reader.

All test compounds were dissolved in DMSO at a concentration of 10mM and were
10 prepared in 100% DMSO using a 1 in 4 dilution step to provide 11 point dose response curves. The dilutions were transferred to the assay plates ensuring that the DMSO concentration was constant across the plate for all assays.

All data was normalized to the mean of 16 high and 16 low control wells on each plate. A four parameter curve fit was then applied.

15

Alternative method for S1P1 GTP γ S assay

S₁P₁ expressing RH7777 membranes (1.5 μ g/well) membranes (1.5 μ g/well) were homogenised by passing through a 23G needle. These were then adhered to WGA-coated SPA beads (0.125mg/well) in assay buffer (HEPES 20mM, MgCl₂ 10mM,
20 NaCl 100mM and pH adjusted to 7.4 using KOH 5M). GDP 10 μ M FAC and saponin 90 μ g/ml FAC were also added.

After 30 minutes precoupling on ice, the bead and membrane suspension was dispensed into white Greiner polypropylene LV 384-well plates (5 μ l/well), containing
25 0.1 μ l of compound. 5 μ l/well [³⁵S]-GTP γ S (0.5nM for S₁P₁ or 0.3nM for S₁P₃ final radioligand concentration) made in assay buffer was then added to the plates. The final assay cocktail (10.1 μ l) was then sealed, spun on a centrifuge, then read immediately on a Viewlux instrument.

30 Exemplified compounds of the invention had a pEC₅₀ > 5. Examples 1-7, 8, 9, 11-13 had a pEC₅₀ of >7. Examples 2, 4, 6 and 8 had a pEC₅₀ of >8,

S1P3

S1P3 membranes from rat basophilic leukaemia cells (RBL-2H3)(1.5µg/well) were adhered to WGA-coated SPA beads (0.125mg/well) in assay buffer (HEPES 20mM, MgCl₂ 3mM, NaCl 100mM and pH adjusted to 7.4 using KOH 5M), GDP 10µM FAC and saponin 90µg/ml FAC was also added).

- 5 After 30 minutes pre-coupling on ice the bead and membrane suspension was dispensed into a white Greiner polypropylene LV384-well plate (5µl/well), containing 0.1µl of the compound. 5µl/well [³⁵S]-GTPγS (0.5nM final radioligand conc) made up in assay buffer was then added to agonist plates. The final assay cocktail (10.1µl) was centrifuged at 1000rpm for 5 minutes then read immediately on a Viewlux
- 10 reader.

All test compounds were dissolved in DMSO at a concentration of 10mM and were prepared in 100% DMSO using a 1 in 4 dilution step to provide 11 point dose response curves. The dilutions were transferred to the assay plates ensuring that the DMSO concentration was constant across the plate for all assays.

- 15 All data was normalized to the mean of 16 high and 16 low control wells on each plate. A four parameter curve fit was then applied.

Alternative method for S1P3 GTPγS assay

S₁P₃ expressing RBL membranes (1.5µg/well) were homogenised by passing

20 through a 23G needle. These were then adhered to WGA-coated SPA beads (0.125mg/well) in assay buffer (HEPES 20mM, MgCl₂ 10mM, NaCl 100mM and pH adjusted to 7.4 using KOH 5M). GDP 10µM FAC and saponin 90µg/ml FAC were also added

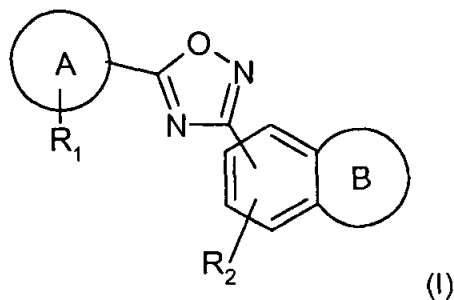
- After 30 minutes precoupling on ice, the bead and membrane suspension was
- 25 dispensed into white Greiner polypropylene LV 384-well plates (5µl/well), containing 0.1µl of compound. 5µl/well [³⁵S]-GTPγS (0.5nM for S₁P₁ or 0.3nM for S₁P₃ final radioligand concentration) made in assay buffer was then added to the plates. The final assay cocktail (10.1µl) was then sealed, spun on a centrifuge, then read immediately on a Viewlux instrument.

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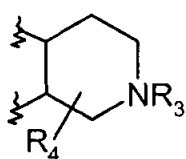
Exemplified compounds tested in this assay had a pEC₅₀ < 6, many had a pEC₅₀ < 5. Examples 1, 4, 8-10, 12 and 13 had a pEC₅₀ < 5.

Claims

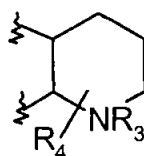
- 5 1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



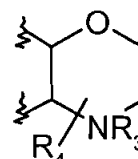
- A is phenyl or a 5 or 6-membered heteroaryl ring;
 R₁ is up to two substituents independently selected from halogen, C₍₁₋₃₎alkoxy, C₍₁₋₃₎fluoroalkyl, cyano, C₍₁₋₃₎fluoroalkoxy, C₍₁₋₆₎alkyl and C₍₃₋₆₎cycloalkyl;
 10 R₂ is hydrogen, halogen or C₍₁₋₄₎alkyl;
 B is selected from one of the following:



(a)



(b)



(c)

- 15 R₃ is hydrogen, C₍₁₋₃₎alkyl or (CH₂)₁₋₃CO₂H;
 R₄ is hydrogen or C₍₁₋₃₎alkyl;
 when R₂ or R₄ is alkyl it may be optionally interrupted by oxygen.
2. A compound of formula (I) or a pharmaceutically acceptable salt thereof,
 20 wherein:
 A is phenyl;
 R₁ is up to two substituents independently selected from chloro, isopropoxy, and cyano;
 R₂ is hydrogen or methyl ;
 25 B is (a);
 R₃ is hydrogen, methyl or (CH₂)₁₋₃CO₂H;
 R₄ is hydrogen.

J6

3. A compound selected from:

5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,3,4-tetrahydroisoquinoline

5

2-[(1-methylethyl)oxy]-5-[3-(1,2,3,4-tetrahydro-5-isoquinoliny)-1,2,4-oxadiazol-5-yl]benzonitrile

[5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1H)-isoquinoliny]acetic acid

10

3-[5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1H)-isoquinoliny]propanoic acid

15

4-[5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1H)-isoquinoliny]butanoic acid

2-[(1-methylethyl)oxy]-5-[3-(2-methyl-1,2,3,4-tetrahydro-5-isoquinoliny)-1,2,4-oxadiazol-5-yl]benzonitrile

20

[8-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2H-chromen-4-yl]acetic acid

3-[6-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinoliny]propanoic acid

25

[6-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinoliny]acetic acid

30

6-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-1,2,3,4-tetrahydroisoquinoline

2-[(1-Methylethyl)oxy]-5-[3-(5-methyl-1,2,3,4-tetrahydro-6-isoquinoliny)-1,2,4-oxadiazol-5-yl]benzonitrile

35

[6-(5-{3-Cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinoliny]acetic acid

57

3-[6-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinoliny]propanoic acid

and pharmaceutically acceptable salts thereof.

5

4. Use of a compound according to any one of claims 1 to 3 for the treatment of conditions or disorders mediated by S1P1 receptors.

5. Use according to claim 4, wherein the condition or disorder is multiple sclerosis, autoimmune diseases, chronic inflammatory disorders, asthma, inflammatory neuropathies, arthritis, transplantation, Crohn's disease, ulcerative colitis, lupus erythematosus, psoriasis, ischemia-reperfusion injury, solid tumours, and tumour metastasis, diseases associated with angiogenesis, vascular diseases, pain conditions, acute viral diseases, inflammatory bowel conditions, insulin and non-insulin dependant diabetes.

10
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6. Use according to claim 4, wherein the condition is lupus erythematosus.

7. Use of a compound according to any one of claims 1 to 3 to manufacture a medicament for use in the treatment of conditions or disorders mediated by S1P1 receptors.

20

8. Use according to claim 7, wherein the condition or disorder multiple sclerosis, autoimmune diseases, chronic inflammatory disorders, asthma, inflammatory neuropathies, arthritis, transplantation, Crohn's disease, ulcerative colitis, lupus erythematosus, psoriasis, ischemia-reperfusion injury, solid tumours, and tumour metastasis, diseases associated with angiogenesis, vascular diseases, pain conditions, acute viral diseases, inflammatory bowel conditions, insulin and non-insulin dependant diabetes.

25
30

9. Use according to claim 7, wherein the condition is lupus erythematosus.

10. A pharmaceutical composition comprising a compound according to any one of claims 1 to 3.

35



11. A method of treatment for conditions or disorders in mammals including humans which can be mediated via the S1P1 receptors which comprises administering to the sufferer a therapeutically safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

5

12. A method of treatment according to claim 11, wherein the condition is lupus erythematosus.

JA

DERIVADOS DE OXADIAZOL ACTIVOS EN 1-FOSFATO DE
ESFINGOSINA

MEMORIA DESCRIPTIVA

5

La presente invención se refiere a derivados de oxadiazol novedosos que tienen actividad farmacológica, procedimientos para su preparación, composiciones farmacéuticas que los contienen y su uso en el tratamiento de diversos trastornos.

10

El 1-fosfato de esfingosina (S1P) es un mediador de lípidos bioactivo formado por la fosforilación de esfingosina por esfingosina cinasas y se encuentra en niveles altos en la sangre. Es producido y secretado por muchos tipos de células, incluyendo aquellos de origen hematopoyético tales como plaquetas y mastocitos (Okamoto et al 1998 J Biol Chem 273(42):27104; Sanchez y Hla 2004, J Cell Biochem 92:913). Tiene un rango amplio de acciones biológicas, incluyendo regulación de la proliferación celular, diferenciación, motilidad, vascularización y activación de células inflamatorias y plaquetas (Pyne y Pyne 2000, Biochem J. 349: 385). Cinco subtipos de receptor que responde a S1P han sido descritos, S1P1 (Edg-1), 15 S1P2 (Edg-5), S1P3 (Edg-3), S1P4 (Edg-6) y S1P5 (Edg-8), que forman parte de la familia de receptores del gen de diferenciación endotelial acoplado a proteína G (Chun et al 2002 Pharmacological Reviews 54:265, Sanchez y Hla 2004 J Cellular Biochemistry, 92:913). Estos 5 receptores muestran expresión

20

de ARNm diferencial, en donde S1P1-3 está altamente expresado, S1P4 está expresado en tejidos linfoides y hematopoyéticos y S1P5 principalmente en el cerebro y a un grado menor en el bazo. Señalizan vía diferentes subseries de proteínas G para promover una variedad de respuestas biológicas (Kluk y Hla
5 2002 Biochem et Biophysica Acta 1582:72, Sanchez y Hla 2004, J Cellular Biochem 92:913).

Papeles propuestos para el receptor S1P1 incluyen tráfico de linfocitos, inducción/supresión de citocinas y efectos en células endoteliales (Rosen y Goetzl 2005 Nat Rev Immunol. 5:560). Agonistas del receptor S1P1
10 se han usado en muchos modelos animales autoinmunes y de transplante, incluyendo Encefalomiелitis Autoimmune Experimental (EAE) de EM, para reducir la gravedad de la enfermedad inducida (Brinkman et al 2003 JBC 277:21453; Fujino et al 2003 J Pharmacol Exp Ther 305:70; Webb et al 2004 J Neuroimmunol 153:108; Rausch et al 2004 J Magn Reson Imaging 20:16). Se
15 informa que esta actividad está mediada por el efecto de agonistas de S1P1 en la circulación de linfocitos a través del sistema linfático. El tratamiento con agonistas de S1P1 da por resultado el secuestro de linfocitos dentro de órganos linfoides secundarios tales como los nódulos linfáticos, induciendo una linfopenia periférica reversible en modelos animales (Chiba et al 1998, J
20 Immunology 160:5037, Forrest et al 2004 J Pharmacol Exp Ther 309:758; Sanna et al 2004 JBC 279:13839). Los datos publicados sobre agonistas sugieren que el tratamiento combinado induce pérdida del receptor S1P1 de la superficie de la células vía internalización (Graler y Goetzl 2004 FASEB J

18:551; Matloubian et al 2004 Nature 427:355; Jo et al 2005 Chem Biol 12:703) y es esta reducción del receptor S1P1 en células inmunes lo que contribuye a la reducción del movimiento de células T de los nódulos linfáticos de vuelta a la corriente sanguínea.

5 La delección del gen S1P1 causa letalidad embrionaria. Experimentos para examinar el papel del receptor S1P1 en la migración y tráfico de linfocitos han incluido la transferencia adoptiva de células T con deficiencia de S1P1 marcadas en ratones tipo silvestre irradiados. Estas células mostraron una salida reducida de órganos linfoides secundarios
10 (Matloubian et al 2004 Nature 427:355).

 A S1P1 se le ha atribuido también un papel en la modulación de la unión de células endoteliales (Allende et al 2003 102:3665, Blood Singelton et al 2005 FASEB J 19:1646). Con respecto a esta acción endotelial, se ha informado que los agonistas de S1P1 tienen un efecto en nódulos linfáticos
15 aislados que puede estar contribuyendo a un papel en la modulación de trastornos inmunes. Los agonistas de S1P1 causaron un cierre de las 'puertas' estromales endoteliales de los senos linfáticos que drenan los nódulos linfáticos y previenen la salida de linfocitos (Wei et al 2005, Nat. Immunology 6:1228).

20 Se ha demostrado que el compuesto inmunosupresor FTY720 (JP11080026-A) reduce los linfocitos circulantes en animales y el hombre, tiene actividad moduladora de enfermedades en modelos animales de trastornos inmunes y reduce los índices de remisión en Esclerosis Múltiple

recurrente remitente (Brinkman et al 2002 JBC 277:21453, Mandala et al 2002 Science 296:346, Fujino et al 2003 J Pharmacology and Experimental Therapeutics 305:45658, Brinkman et al 2004 American J Transplantation 4:1019, Webb et al 2004 J Neuroimmunology 153:108, Morris et al 2005 EurJ
5 Immunol 35:3570, Chiba 2005 Pharmacology and Therapeutics 108:308, Kahan et al 2003, Transplantation 76:1079, Kappos et al 2006 New Eng J Medicine 335:1124). Este compuesto es un profármaco que es fosforilado *in vivo* por esfingosina cinasas para dar una molécula que tiene actividad agonista en los receptores S1P1, S1P3, S1P4 y S1P5. Estudios clínicos han
10 demostrado que el tratamiento con FTY720 da por resultado bradicardia en las primeras 24 horas de tratamiento (Kappos et al 2006 New Eng J Medicine 335:1124). Se cree que la bradicardia se debe a agonismo en el receptor S1P3, con base en muchos experimentos basados en células y experimentos animales. Estos incluyen el uso de animales con bloqueo de genes ("knock-
15 out") S1P3 los cuales, a diferencia de los ratones tipo silvestre, no demuestran bradicardia después de la administración de FTY720 y el uso de compuestos selectivos con respecto a S1P1 (Hale et al 2004 Bioorganic & Medicinal Chemistry Letters 14:3501, Sanna et al 2004 JBC 279:13839, Koyrakh et al 2005 American J Transplantation 5:529).

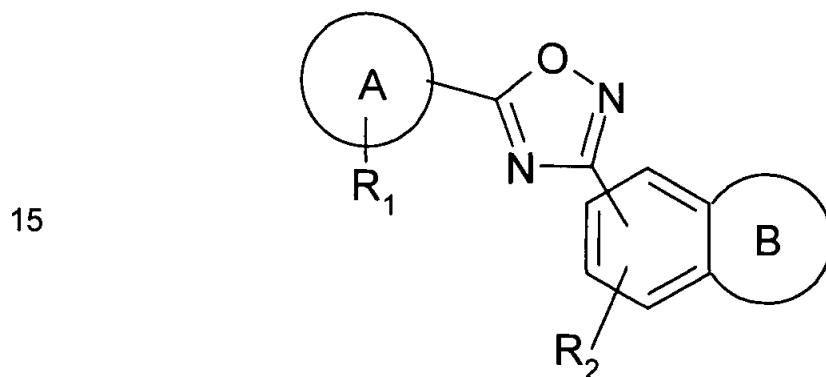
20 Por ende, existe la necesidad de compuestos agonistas del receptor S1P1 con selectividad con respecto a S1P3 que se pueda esperar que muestren una tendencia reducida a inducir bradicardia.

Las siguientes solicitudes de patente describen derivados de oxadiazol como agonistas de S1P1: WO03/105771, WO05/058848, WO06/047195, WO06/100633, WO06/115188, WO06/131336, WO07/024922 y WO07/116866.

5 Las siguientes solicitudes de patente describen derivados de tetrahidroisoquinolinil-oxadiazol como agonistas del receptor S1P: WO06/064757, WO06/001463, WO04/113330.

Ahora se ha encontrado una clase estructuralmente novedosa de compuestos que provee agonistas del receptor S1P1.

10 Por lo tanto, la presente invención provee compuestos de fórmula (I) o una sal farmacéuticamente aceptable de los mismos:



(I)

A es fenilo o un anillo de heteroarilo de 5 o 6 eslabones;

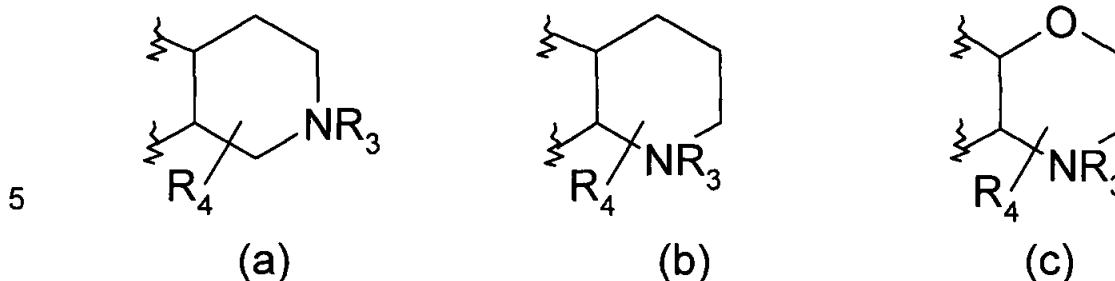
20 R₁ es hasta dos sustituyentes seleccionados independientemente de halógeno, alcoxi C₍₁₋₃₎, fluoroalquilo C₍₁₋₃₎, ciano, fluoroalcoxi C₍₁₋₃₎, alquilo C₍₁₋₆₎ y cicloalquilo C₍₃₋₆₎;

R₂ es hidrógeno, halógeno o alquilo C₍₁₋₄₎;

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6

B se selecciona de uno de los siguientes:



R_3 es hidrógeno, alquilo $C_{(1-3)}$ o $(CH_2)_{1-3}CO_2H$;

R_4 es hidrógeno o alquilo $C_{(1-3)}$;

10 cuando R_2 o R_4 es alquilo puede ser interrumpido opcionalmente por oxígeno.

En una modalidad de la invención,

A es fenilo; y/o

15 R_1 es hasta dos sustituyentes independientemente seleccionados de cloro, isopropoxi y ciano; y/o

R_2 es hidrógeno; y/o

B es (a); y/o

R_3 es hidrógeno, metilo o $(CH_2)_{1-3}CO_2H$; y/o

R_4 es hidrógeno.

20 A es fenilo;

R_1 es hasta dos sustituyentes independientemente seleccionados de cloro, isopropoxi y ciano;

R_2 es hidrógeno o metilo;

B es (a);

R₃ es hidrógeno, metilo o (CH₂)₁₋₃CO₂H;

R₄ es hidrógeno.

En una modalidad A es fenilo. En otra modalidad A es fenilo 3,4-
5 disustituido.

En una modalidad R₁ es dos sustituyentes uno de los cuales es
alcoxi C₍₁₋₃₎, el otro seleccionado de halógeno o ciano. En otra modalidad R₁
es dos sustituyentes, uno de los cuales es isopropoxi y el otro es seleccionado
de cloro o ciano. En otra modalidad, R₁ es dos sustituyentes seleccionados de
10 cloro, isopropoxi y ciano. En otra modalidad R₁ es cloro e isopropoxi. En otra
modalidad R₁ es cloro en la posición 3 e isopropoxi en la posición 4 cuando A
es fenilo. En otra modalidad R₁ es isopropoxi y ciano. En otra modalidad R₁ es
ciano en la posición 3 e isopropoxi en la posición 4 cuando A es fenilo.

En una modalidad R₂ es hidrógeno o metilo.

15 En una modalidad B es (a).

En una modalidad R₃ es hidrógeno, metilo o (CH₂)₁₋₃CO₂H.

En una modalidad R₄ es hidrógeno.

El término "alquilo" como un grupo o parte de un grupo, por
ejemplo, alcoxi o hidroxialquilo se refiere a un grupo alquilo recto o ramificado
20 en todas las formas isoméricas. El término "alquilo C₍₁₋₆₎" se refiere a un grupo
alquilo, como se define anteriormente, que contiene al menos 1, y como
máximo 6 átomos de carbono. Ejemplos de tales grupos alquilo incluyen
metilo, etilo, propilo, iso-propilo, n-butilo, iso-butilo, sec-butilo o ter-butilo.

Ejemplos de tales grupos alcoxi incluyen metoxi, etoxi, propoxi, iso-propoxi, butoxi, iso-butoxi, sec-butoxi y ter-butoxi.

Grupos cicloalquilo $C_{(3-6)}$ adecuados incluyen ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo.

5 Como se usa en la presente, el término "halógeno" se refiere a flúor (F), cloro (Cl), bromo (Br), o yodo (I) y el término "halo" se refiere al halógeno: fluoro (-F), cloro (-Cl), bromo (-Br) y yodo (-I).

El término "heteroarilo" representa un anillo insaturado que comprende uno o más heteroátomos seleccionados de O, N o S. Ejemplos de
10 anillos de heteroarilo de 5 o 6 eslabones incluyen pirrolilo, triazolilo, tiadiazolilo, tetrazolilo, imidazolilo, pirazolilo, isotiazolilo, tiazolilo, isoxazolilo, oxazolilo, oxadiazolilo, furazanilo, furanilo, tienilo, piridilo, pirimidínilo, pirazinilo, piridazinilo y triazinilo.

En algunos de los compuestos de fórmula (I), dependiendo de la
15 naturaleza del sustituyente, hay átomos de carbono quirales y, por lo tanto, los compuestos de fórmula (I) pueden existir como estereoisómeros. La invención se extiende a todos los isómeros ópticos tales como formas estereoisoméricas de los compuestos de fórmula (I) incluyendo enantiómeros, diastereoisómeros y mezclas de los mismos, tales como racematos. Las diferentes formas
20 estereoisoméricas pueden ser separadas o resueltas unas de otras por medio de métodos convencionales o cualquier isómero dado se puede obtener mediante síntesis estereoselectiva o síntesis asimétrica convencionales.

Algunos de los compuestos en la presente pueden existir en diversas formas tautoméricas y se debe entender que la invención incluye todas esas formas tautoméricas.

Se entiende que ciertos compuestos de la invención contienen
5 grupos tanto ácidos como básicos y, por lo tanto, pueden existir como zwitteriones a ciertos valores de pH.

Compuestos adecuados de la invención son:

5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,3,4-tetrahydroisoquinolina

10 2-[(1-metiletil)oxi]-5-[3-(1,2,3,4-tetrahydro-5-isoquinolinil)-1,2,4-oxadiazol-5-il]benzonitrilo

ácido [5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-3,4-dihidro-2(1H)-isoquinolinil]acético

15 ácido 3-[5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-3,4-dihidro-2(1H)-isoquinolinil]propanoico

ácido 4-[5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-3,4-dihidro-2(1H)-isoquinolinil]butanoico

2-[(1-metiletil)oxi]-5-[3-(2-metil-1,2,3,4-tetrahydro-5-isoquinolinil)-1,2,4-oxadiazol-5-il]benzonitrilo

20 ácido [8-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-3,4-dihidro-2H-cromen-4-il]acético

ácido 3-[6-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-5-metil-3,4-dihidro-2(1H)-isoquinolinil]propanoico

ácido [6-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-5-metil-3,4-dihidro-2(1H)-isoquinolinil]acético

6-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-5-metil-1,2,3,4-tetrahidroisoquinolina

5 2-[(1-Metiletil)oxi]-5-[3-(5-metil-1,2,3,4-tetrahidro-6-isoquinolinil)-1,2,4-oxadiazol-5-il]benzonitrilo

ácido [6-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-5-metil-3,4-dihidro-2(1H)-isoquinolinil]acético

10 ácido 3-[6-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-5-metil-3,4-dihidro-2(1H)-isoquinolinil]propanoico

o sales farmacéuticamente aceptable de los mismos.

Derivados farmacéuticamente aceptables de los compuestos de fórmula (I) incluyen cualquier sal farmacéuticamente aceptable, éster o sal de dicho éster de un compuesto de fórmula (I) que, tras la administración al sujeto que lo recibe es capaz de proveer (directa o indirectamente) un
15 compuesto de fórmula (I) o un metabolito activo o residuo del mismo.

Los compuestos de fórmula (I) pueden formar sales. Se entenderá que para usar en medicina las sales de los compuestos de fórmula (I) deben ser farmacéuticamente aceptables. Sales farmacéuticamente
20 aceptables adecuadas serán evidentes para los expertos en la técnica e incluyen aquellas que se describen en J. Pharm. Sci., 1977, 66, 1-19, tales como sales ácidas de adición formadas con ácidos inorgánicos, por ejemplo, ácido clorhídrico, bromhídrico, sulfúrico, nítrico o fosfórico; y ácidos orgánicos,

por ejemplo, ácido succínico, maleico, acético, fumárico, cítrico, tartárico, benzoico, p-toluensulfónico, metansulfónico o naftalensulfónico. Algunos de los compuestos de fórmula (I) pueden formar sales ácidas de adición con uno o más equivalentes del ácido. La presente invención incluye dentro de su

5 alcance todas las formas estequiométricas y no estequiométricas posibles. También se pueden preparar sales a partir de bases farmacéuticamente aceptables incluyendo bases inorgánicas y bases orgánicas. Sales derivadas de bases inorgánicas incluyen sales de aluminio, amonio, calcio, cobre, férrica, ferrosa, de litio, de magnesio, mangánica, manganosa, de potasio, de

10 sodio, zinc y similares. Sales derivadas de bases orgánicas farmacéuticamente aceptables incluyen sales de aminas primarias, secundarias y terciarias; aminas sustituidas incluyendo aminas sustituidas naturales, y aminas cíclicas. Bases orgánicas farmacéuticamente aceptables particulares incluyen arginina, betaína, cafeína, colina, N,N'-

15 dibenciletilendiamina, dietilamina, 2-dietilaminoetanol, 2-dimetilaminoetanol, etanolamina, etilendiamina, N-etil-morfolina, N-etilpiperidina, glucamina, glucosamina, histidina, hidrabamina, isopropilamina, lisina, metilglucamina, morfolina, piperazina, piperidina, procaína, purinas, teobromina, trietilamina, trimetilamina, tripropilamina, tris(hidroximetil)aminometano (TRIS, trometamol)

20 y similares. Asimismo se pueden formar sales a partir de resinas de intercambio de iones básicas, por ejemplo, resinas de poliamina. Cuando el compuesto de la presente invención es básico, las sales se pueden preparar a partir de ácidos farmacéuticamente aceptables, incluyendo ácidos inorgánicos

y ácidos orgánicos. Tales ácidos incluyen ácido acético, bencensulfónico, benzoico, canforsulfónico, cítrico, etansulfónico, etandisulfónico, fumárico, glucónico, glutámico, bromhídrico, clorhídrico, isetiónico, láctico, maleico, málico, mandélico, metansulfónico, mícico, pamoico, pantoténico, fosfórico, propiónico, succínico, sulfúrico, tartárico, p-toluensulfónico y similares.

Sales de adición farmacéuticamente aceptables se pueden preparar de manera convencional mediante reacción con el ácido o derivado de ácido apropiado. Sales farmacéuticamente aceptables con bases se pueden preparar convencionalmente mediante reacción con la base inorgánica u orgánica apropiada.

Los compuestos de fórmula (I) se pueden preparar en forma cristalina o no cristalina, y, si es cristalina, pueden ser opcionalmente hidratados o solvatados. Esta invención incluye dentro de su alcance hidratos o solvatos estequiométricos así como compuestos que contienen cantidades variables de agua y/o solvente.

Dentro del alcance de la invención se incluyen todas las sales, solvatos, hidratos, complejos, polimorfos, profármacos, derivados radiomarcados, estereoisómeros e isómeros ópticos de los compuestos de fórmula (I).

Las potencias y eficacias de los compuestos de esta invención para el receptor S1P1 se pueden determinar mediante ensayo GTPγS realizado en el receptor clonado de humano como se describe en la presente.

Los compuestos de fórmula (I) han demostrado actividad agonista en el receptor S1P1, usando ensayos funcionales descritos en la presente.

Por lo tanto, los compuestos de fórmula (I) y sus sales farmacéuticamente aceptables son útiles en el tratamiento de condiciones o

5 trastornos que son mediados vía el receptor S1P1. En particular los compuestos de fórmula (I) y sus sales farmacéuticamente aceptables son útiles en el tratamiento de esclerosis múltiple, enfermedades autoinmunes, trastornos inflamatorios crónicos, asma, neuropatías inflamatorias, artritis, trasplante, enfermedad de Crohn, colitis ulcerativa, lupus eritematoso,

10 psoriasis, lesión por reperusión por isquemia, tumores sólidos y metástasis tumoral, enfermedades asociadas con angiogénesis, enfermedades vasculares, condiciones de dolor, enfermedades virales agudas, condiciones inflamatorias del intestino, diabetes dependiente de insulina y no dependiente de insulina (en adelante llamados los "trastornos de la invención").

15 Por lo tanto, los compuestos de fórmula (I) y sus sales farmacéuticamente aceptables son útiles en el tratamiento de lupus eritematoso.

Por ende, los compuestos de fórmula (I) y sus sales farmacéuticamente aceptables son útiles en el tratamiento de la psoriasis.

20 Por consiguiente, los compuestos de fórmula (I) y sus sales farmacéuticamente aceptables son útiles en el tratamiento de esclerosis múltiple.

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Se debe entender que "tratamiento" como se usa en la presente incluye profilaxis así como alivio de síntomas establecidos.

Por ende, la invención provee también compuestos de fórmula (I) o sales farmacéuticamente aceptables de los mismos, para usar como
5 sustancias terapéuticas, en particular en el tratamiento de las condiciones o trastornos mediados vía el receptor S1P1. En particular la invención provee un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo para usar como una sustancia terapéutica en el tratamiento de esclerosis múltiple, enfermedades autoinmunes, trastornos inflamatorios crónicos, asma,
10 neuropatías inflamatorias, artritis, trasplante, enfermedad de Crohn, colitis ulcerativa, lupus eritematoso, psoriasis, lesión por reperfusión por isquemia, tumores sólidos y metástasis tumoral, enfermedades asociadas con angiogénesis, enfermedades vasculares, condiciones de dolor, enfermedades virales agudas, condiciones inflamatorias del intestino, diabetes dependiente
15 de insulina y no dependiente de insulina.

Los compuestos de fórmula (I) y sus sales farmacéuticamente aceptables son útiles como sustancias terapéuticas en el tratamiento de lupus eritematoso.

Los compuestos de fórmula (I) y sus sales farmacéuticamente
20 aceptables son útiles como sustancias terapéuticas en el tratamiento de la psoriasis.

Los compuestos de fórmula (I) y sus sales farmacéuticamente aceptables son útiles como sustancias terapéuticas en el tratamiento de esclerosis múltiple.

La invención provee además un método de tratamiento de

5 condiciones o trastornos en mamíferos incluyendo humanos que pueden ser mediados vía el receptor S1P1, que comprende administrar al sujeto que padece la condición o trastorno una cantidad terapéuticamente segura y efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo. En particular, la invención provee un método de

10 tratamiento de esclerosis múltiple, enfermedades autoinmunes, trastornos inflamatorios crónicos, asma, neuropatías inflamatorias, artritis, trasplante, enfermedad de Crohn, colitis ulcerativa, lupus eritematoso, psoriasis, lesión por reperfusión por isquemia, tumores sólidos y metástasis tumoral, enfermedades asociadas con angiogénesis, enfermedades vasculares,

15 condiciones de dolor, enfermedades virales agudas, condiciones inflamatorias del intestino, diabetes dependiente de insulina y no dependiente de insulina, que comprende administrar al sujeto que padece la condición o trastorno una cantidad terapéuticamente segura y efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo.

20 La invención provee un método de tratamiento de lupus eritematoso, que comprende administrar al sujeto que lo padece una cantidad terapéuticamente segura y efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo.

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La invención provee un método de tratamiento de la psoriasis, que comprende administrar al sujeto que la padece una cantidad terapéuticamente segura y efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo.

- 5 La invención provee un método de tratamiento de esclerosis múltiple, que comprende administrar al sujeto que la padece una cantidad terapéuticamente segura y efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo.

En otro aspecto, la invención prevé el uso de un compuesto de
10 fórmula (I) o una sal farmacéuticamente aceptable del mismo en la fabricación de un medicamento para usar en el tratamiento de las condiciones o trastornos mediados vía el receptor S1P1.

En particular la invención provee un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo para usar en la fabricación de,
15 un medicamento para usar en el tratamiento de esclerosis múltiple, enfermedades autoinmunes, trastornos inflamatorios crónicos, asma, neuropatías inflamatorias, artritis, trasplante, enfermedad de Crohn, colitis ulcerativa, lupus eritematoso, psoriasis, lesión por reperfusión por isquemia, tumores sólidos y metástasis tumoral, enfermedades asociadas con
20 angiogénesis, enfermedades vasculares, condiciones de dolor, enfermedades virales agudas, condiciones inflamatorias del intestino, diabetes dependiente de insulina y no dependiente de insulina.

Los compuestos de fórmula (I) y sus sales farmacéuticamente aceptables son útiles en la fabricación de un medicamento para usar en el tratamiento de lupus eritematoso.

Los compuestos de fórmula (I) y sus sales farmacéuticamente
5 aceptables son útiles en la fabricación de un medicamento para usar en el tratamiento de la psoriasis.

Los compuestos de fórmula (I) y sus sales farmacéuticamente aceptables son útiles en la fabricación de un medicamento para usar en el tratamiento de esclerosis múltiple.

10 A fin de usar los compuestos de fórmula (I) y sales farmacéuticamente aceptables de los mismos en terapia, normalmente serán formulados en una composición farmacéutica de acuerdo con la práctica farmacéutica estándar. La presente invención provee también una composición farmacéutica, la cual comprende un compuesto de fórmula (I) o
15 una sal farmacéuticamente aceptable del mismo, y un vehículo o excipiente farmacéuticamente aceptable.

En otro aspecto, la presente invención provee un procedimiento para preparar una composición farmacéutica, el procedimiento comprende mezclar un compuesto de fórmula (I) o una sal farmacéuticamente aceptable
20 del mismo y un vehículo o excipiente farmacéuticamente aceptable.

Una composición farmacéutica de la invención, la cual se puede preparar mediante mezcla, de manera adecuada a temperatura ambiente y presión atmosférica, es usualmente adaptada para administración oral,

parenteral o rectal y, como tal, puede ser en forma de tabletas, cápsulas, preparaciones líquidas orales, polvos, gránulos, pastillas, polvos reconstituibles, soluciones inyectables o para infusiones o suspensiones o supositorios. Generalmente se prefieren composiciones administrables
5 oralmente.

Las tabletas y cápsulas para administración oral pueden ser en forma de dosis unitaria, y pueden contener excipientes convencionales, tales como agentes aglutinantes (por ejemplo, almidón de maíz pregelatinizado, polivinilpirrolidona o hidroxipropilmetilcelulosa); llenadores (por ejemplo,
10 lactosa, celulosa microcristalina o bifosfato de calcio), lubricantes de tableteado (por ejemplo, estearato de magnesio, talco o sílice); desintegrantes (por ejemplo, almidón de papa o glicolato de almidón de sodio); y agentes humectantes aceptables (por ejemplo, laurilsulfato de sodio). Las tabletas pueden ser revestidas de acuerdo con métodos bien conocidos en la práctica
15 farmacéutica normal.

Preparaciones líquidas orales pueden ser en forma de, por ejemplo, suspensiones, soluciones, emulsiones, jarabes o elixires acuosos u oleosos, o pueden ser en forma de un producto seco para reconstitución con agua u otro vehículo adecuado antes de usar. Dichas preparaciones líquidas
20 pueden contener aditivos convencionales tales como agentes de suspensión (por ejemplo, jarabe de sorbitol, derivados de celulosa o grasas comestibles hidrogenadas), agentes emulsionantes (por ejemplo, lecitina o acacia), vehículos no acuosos (que pueden incluir aceites comestibles, por ejemplo,

aceite de almendra, ésteres oleosos, alcohol etílico o aceites vegetales fraccionados), conservadores (por ejemplo, metil o propil-p-hidroxibenzoatos o ácido sórbico), y, si se desea, saborizantes o colorantes convencionales, sales reguladoras de pH y agentes edulcorantes como sea apropiado.

- 5 Preparaciones para administración oral se pueden formular de manera adecuada para dar liberación controlada del compuesto activo.

Para administración parenteral, se preparan formas de dosificación unitarias utilizando un compuesto de la invención o sales farmacéuticamente aceptables del mismo y un vehículo estéril. Las

10 formulaciones para inyección se pueden presentar en forma de dosificación unitaria, por ejemplo, en ampollitas o en dosis múltiple, utilizando un compuesto de la invención o derivados farmacéuticamente aceptables del mismo y un vehículo estéril, opcionalmente con un conservador agregado. Las composiciones pueden tomar formas tales como suspensiones, soluciones o

15 emulsiones en vehículos oleosos u acuosos, y pueden contener agentes de formulación tales como agentes de suspensión, estabilización y/o dispersión. De manera alternativa, el ingrediente activo puede estar en forma de polvo para constitución con un vehículo adecuado, por ejemplo, agua libre de pirógenos estéril, antes de usar. El compuesto, dependiendo del vehículo y

20 concentración usados, puede ser ya sea suspendido o disuelto en el vehículo. Al preparar las soluciones, el compuesto se puede disolver para inyección y esterilizar por filtración antes de introducirlo en un vial o ampollita adecuados y sellar. De manera favorable, adyuvantes tales como un anestésico local,

conservadores y agentes reguladores de pH se disuelven en el vehículo. Para mejorar la estabilidad, la composición se puede congelar después de introducirla en el vial y el agua se puede retirar bajo vacío. Las suspensiones parenterales se preparan sustancialmente de la misma manera, excepto que
5 el compuesto es suspendido en el vehículo en lugar de ser disuelto, y la esterilización no se puede realizar por filtración. El compuesto puede ser esterilizado por exposición a óxido de etileno antes de suspensión en un vehículo estéril. De manera favorable, un agente tensoactivo o agente humectante se incluye en la composición para facilitar la distribución uniforme
10 del compuesto.

Se pueden formular lociones con una base acuosa u oleosa y en general contendrán también uno o más agentes emulsionantes, agentes estabilizadores, agentes de dispersión, agentes de suspensión, agentes espesantes o agentes colorantes. Se pueden formular gotas con una base
15 acuosa o no acuosa incluyendo también uno o más agentes de dispersión, agentes estabilizadores, agentes solubilizantes o agentes de suspensión. Asimismo pueden contener un conservador.

Los compuestos de fórmula (I) o sales farmacéuticamente aceptables de los mismos se pueden formular también en composiciones
20 rectales tales como supositorios o enemas de retención, por ejemplo, que contienen bases de supositorios convencionales tales como manteca de cacao u otros glicéridos.

Los compuestos de fórmula (I) o sales farmacéuticamente aceptables de los mismos se pueden formular también como preparaciones de liberación lenta. Tales formulaciones de acción prolongada se pueden administrar mediante implantación (por ejemplo, en forma subcutánea o intramuscular) o mediante inyección intramuscular. Por lo tanto, por ejemplo, los compuestos de la invención se pueden formular con materiales poliméricos o hidrofóbicos adecuados (por ejemplo, como una emulsión en un aceite aceptable) o resinas de intercambio de iones, o como derivados apenas solubles, por ejemplo, como una sal apenas soluble.

Para administración intranasal, los compuestos de fórmula (I) o sales farmacéuticamente aceptables de los mismos, se pueden formular como soluciones para administración vía un dispositivo de dosis medidas en forma adecuada o dispositivo de dosis unitaria o de manera alternativa como una mezcla en polvo con un vehículo adecuado para administración usando un dispositivo de suministro adecuado. Por ende, los compuestos de fórmula (I) o sales farmacéuticamente aceptables de los mismos se pueden formular para administración oral, bucal, parenteral, tópica (incluyendo oftálmica y nasal), de liberación lenta o rectal o en una forma adecuada para administración por inhalación o insuflación (ya sea a través de la boca o nariz).

Los compuestos de fórmula (I) o sales farmacéuticamente aceptables de los mismos se pueden formular para administración tópica en forma de ungüentos, cremas, geles, lociones, pesarios, aerosoles o gotas (por ejemplo, gotas para ojos, oídos o nariz). Los ungüentos y cremas se pueden

formular, por ejemplo, con una base acuosa u oleosa con la adición de agentes espesantes y/o gelificantes adecuados. Los ungüentos para administración a los ojos se pueden fabricar en una manera estéril usando componentes esterilizados.

- 5 La composición puede contener de 0.1% a 99% en peso, de preferencia de 10 a 60% en peso, del material activo, dependiendo del método de administración. La dosis del compuesto usada en el tratamiento de los trastornos antes mencionados variará en la manera usual con la gravedad de los trastornos, el peso del sujeto que padece el trastorno y otros factores
- 10 similares. No obstante, como una guía general dosis unitarias adecuadas pueden ser 0.05 a 1000 mg, 1.0 a 500 mg o 1.0 a 200 mg y dichas dosis unitarias se pueden administrar más de una vez al día, por ejemplo, dos o tres veces al día.

- Los compuestos de fórmula (I) o sales farmacéuticamente
- 15 aceptables de los mismos se pueden usar en preparaciones combinadas. Por ejemplo, los compuestos de la invención se pueden usar en combinación con ciclosporina A, metotrexato, esteroides, rapamicina, inhibidores de citocinas proinflamatorias, inmunomoduladores incluyendo sustancias biológicas u otros compuestos terapéuticamente activos.

- 20 La presente invención incluye también compuestos isotópicamente marcados, que son idénticos a aquellos citados en las fórmulas I y siguientes, excepto por el hecho de que uno o más átomos son reemplazados por un átomo que tiene una masa atómica o número de masa

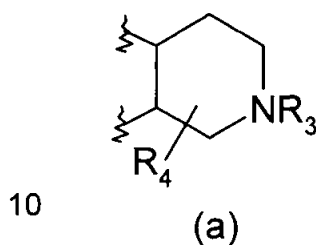
diferente de la masa atómica o número de masa usualmente encontrado en la naturaleza. Ejemplos de isótopos que se pueden incorporar en los compuestos de la invención incluyen isótopos de hidrógeno, carbono, nitrógeno, oxígeno, fósforo, flúor, yodo y cloro, tales como ^3H , ^{11}C , ^{14}C , ^{18}F ,
5 ^{123}I y ^{125}I .

Los compuestos de la presente invención y sales farmacéuticamente aceptables de dichos compuestos que contienen los isótopos antes mencionados y/u otros isótopos de otros átomos se encuentran dentro del alcance de la presente invención. Los compuestos isotópicamente
10 marcados de la presente invención, por ejemplo, aquellos en los cuales isótopos radioactivos tales como ^3H , ^{14}C son incorporados, son útiles en ensayos de distribución de fármacos y/o sustratos en el tejido. Isótopos tritados, es decir, ^3H , y carbono-14, es decir, ^{14}C , son particularmente preferidos por su facilidad de preparación y detectabilidad. Los isótopos ^{11}C y
15 ^{18}F son particularmente útiles en PET (tomografía por emisión de positrones), e isótopos ^{125}I son particularmente útiles en SPECT (tomografía computarizada de emisión de fotones individuales), todos útiles en la obtención de imágenes del cerebro. Además, la sustitución con isótopos más pesados tales como deuterio, es decir, ^2H , puede brindar ciertas ventajas terapéuticas que resultan
20 de una mayor estabilidad metabólica, por ejemplo, vida media *in vivo* incrementada o requerimientos de dosificación reducidos y, por ende, se puede preferir en algunas circunstancias. Los compuestos isotópicamente marcados de fórmula (I) y siguientes de esta invención se pueden preparar

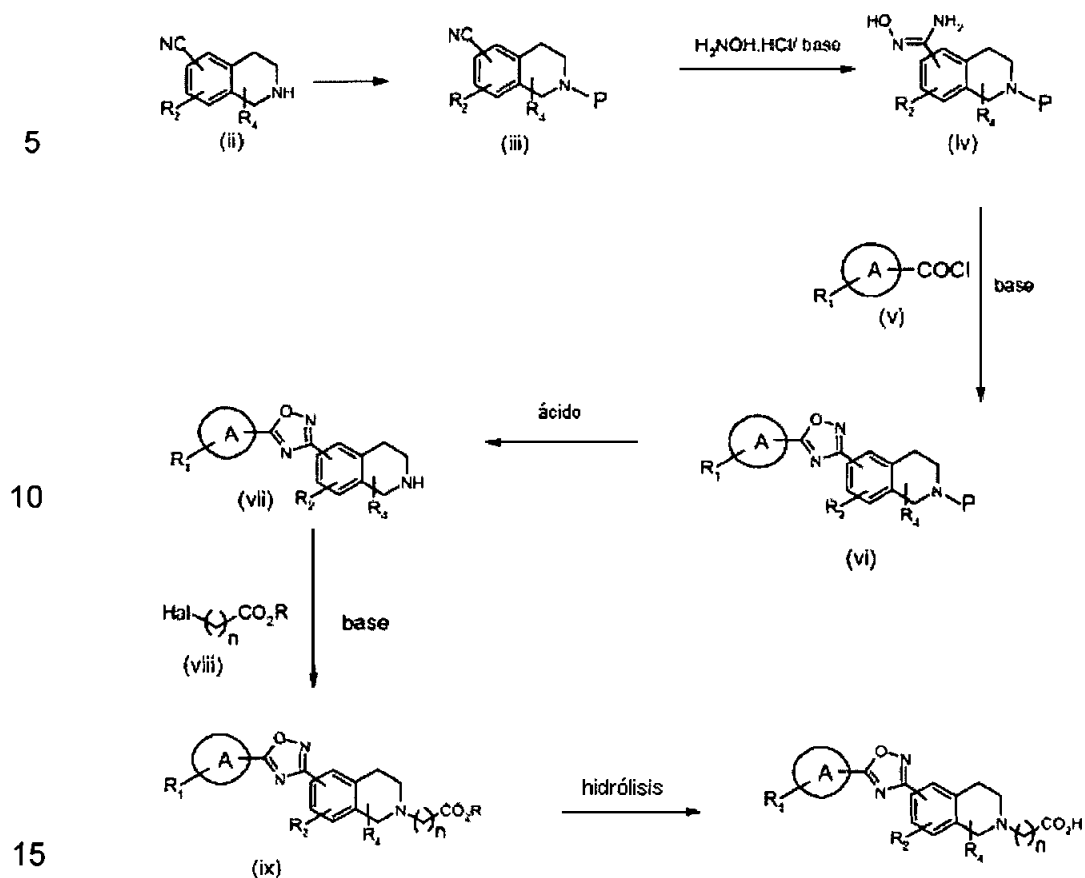
generalmente llevando a cabo los procedimientos descritos en los Esquemas y/o en los Ejemplos más adelante, al sustituir un reactivo isotópicamente marcado fácilmente disponible por un reactivo no isotópicamente marcado.

En otro aspecto, esta invención provee procedimientos para la
5 preparación de un compuesto de fórmula (I).

Compuestos de fórmula (I) en donde B es



y R_3 es $(\text{CH}_2)_{1-3}\text{CO}_2\text{H}$ se pueden preparar de acuerdo con el Esquema 1, en donde R_1 , R_2 , R_4 y A son como se define para la fórmula (I), n
15 es 3, hal es cloro, bromo o yodo, P es un grupo protector y R representa un grupo alquilo (por ejemplo, etilo o ter-butilo).

ESQUEMA 1

Los compuestos de fórmula (ii) (por ejemplo, preparados como se describe en Tetrahedron (2006), 62(29), 6869-6875) se pueden convertir a un derivado protegido adecuado (iii), donde P es, por ejemplo, t-butoxicarbonilo, usando un reactivo protector adecuado tal como dicarbonato de bis(1,1-dimetiletilo). Los compuestos de fórmula (iii) pueden ser convertidos

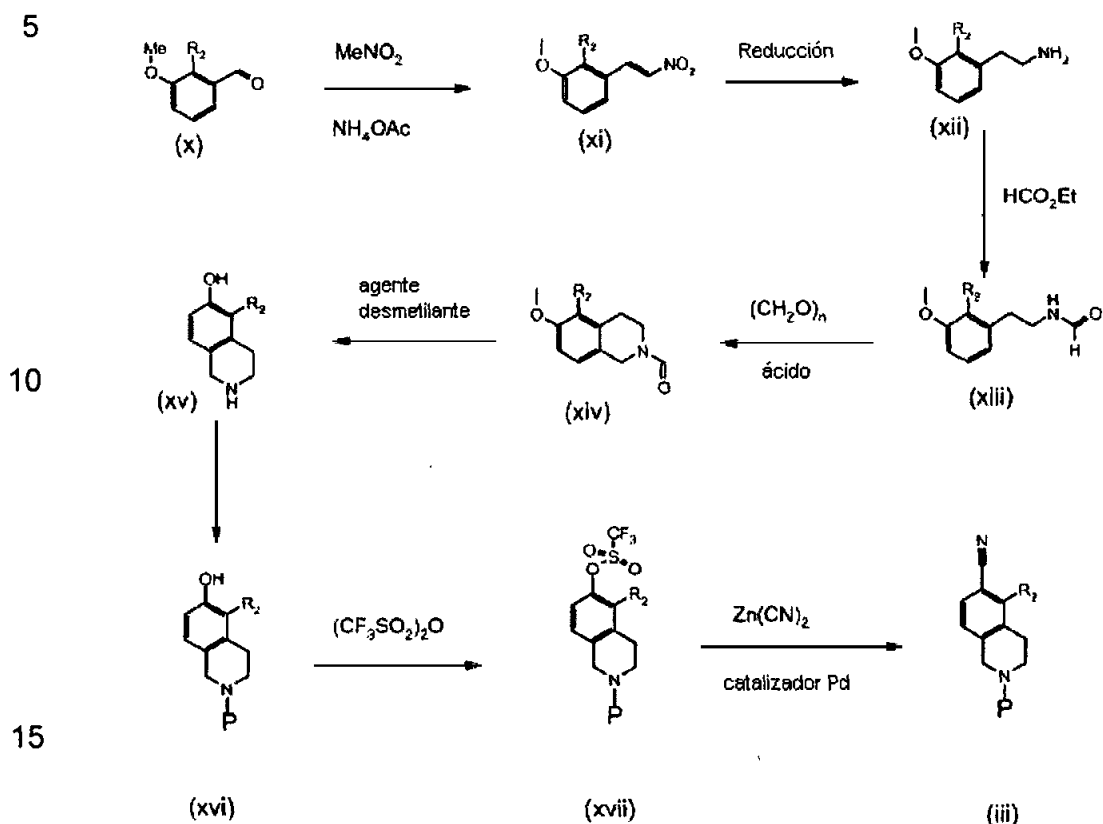
presencia de una base adecuada tal como bicarbonato de sodio. Los compuestos de fórmula (iv) pueden ser convertidos a compuestos de fórmula (vi) mediante reacción con un cloruro de ácido de fórmula (v) en presencia de una base adecuada tal como N,N-diisopropiletilamina, opcionalmente en presencia de un catalizador tal como 4-dimetilaminopiridina. La reacción se puede llevar a cabo a temperatura ambiente inicialmente seguida de calentamiento para efectuar ciclización al oxadiazol. Los compuestos de fórmula (vi) pueden ser desprotegidos para dar compuestos de fórmula (vii), por ejemplo, con un ácido adecuado tal como ácido clorhídrico donde P representa t-butoxicarbonilo. Los compuestos de fórmula (vii) pueden ser convertidos a compuestos de fórmula (ix) mediante reacción con un agente de alquilación de fórmula (viii) en presencia de una base adecuada tal como carbonato de cesio. Los compuestos de fórmula (ix) pueden ser convertidos a ciertos compuestos de fórmula (I) por medio de hidrólisis con una base adecuada tal como hidróxido de litio o (para R = t-butilo) un ácido adecuado tal como ácido clorhídrico o ácido trifluoroacético. Los compuestos de fórmula (v) son ya sea compuestos conocidos o pueden ser preparados por medios convencionales a partir de los ácidos correspondientes, que son en sí mismos ya sea compuestos conocidos o pueden ser preparados por medios convencionales.

Compuestos de fórmula (iii) en donde R_2 está en la posición 5 y el grupo ciano está la posición 6 del sistema de anillo de tetrahydroisoquinolina

85

se pueden preparar como se muestra en el Esquema 2, en donde R_1 es definido para la fórmula (I), R_4 es hidrógeno y P es un grupo protector.

ESQUEMA 2



Los compuestos de la fórmula (x) pueden ser convertidos a compuestos de fórmula (xii) mediante reacción con nitrometano en presencia de una base adecuada tal como acetato de amonio. Los compuestos de fórmula (xi) pueden ser convertidos a compuestos de fórmula (xii) mediante reducción con un agente reductor adecuado tal como borohidruro de litio en

presencia de clorotrimetilsilano. Los compuestos de fórmula (xii) pueden ser convertidos a compuestos de fórmula (xiii) mediante reacción con un agente de formilación adecuado tal como formiato de etilo. Los compuestos de fórmula (xiii) pueden ser convertidos a compuestos de fórmula (xiv) mediante
5 reacción con una fuente de formaldehído adecuada tal como paraformaldehído, en presencia de un catalizador de ácido adecuado tal como ácido fórmico.

Los compuestos de fórmula (xiv) pueden ser convertidos a compuestos de fórmula (xv) mediante reacción con un agente desmetilante
10 adecuado tal como tribromuro de boro.

Los compuestos de fórmula (xv) pueden ser convertidos a derivados protegidos adecuados de fórmula (xvi) donde P es, por ejemplo, t-butoxicarbonilo, usando un reactivo protector adecuado tal como dicarbonato de bis(1,1-dimetiletilo). Los compuestos de fórmula (xvi) pueden ser
15 convertidos a compuestos de fórmula (xvii) por medio de reacción con un agente de trifluorometansulfonilación tal como anhídrido trifluorometansulfónico.

Los compuestos de fórmula (xvii) pueden ser convertidos a compuestos de fórmula (iii) (en donde R_2 está en la posición 5, R_4 es
20 hidrógeno y el grupo ciano está en la posición 6) por medio de reacción con una fuente de cianuro adecuada tal como cianuro de zinc en presencia de un catalizador adecuado tal como tetrakis(trifenilfosfin) paladio (0).

Todas las publicaciones, incluyendo mas no limitadas a patentes y solicitudes de patente, citadas en esta especificación se incorporan en la presente como referencia como si se indicara específica e individualmente que cada publicación individual está incorporada como referencia en la presente como se expone por completo.

Las siguientes descripciones y ejemplos ilustran la preparación de compuestos de la invención.

Abreviaciones

10	g – gramos
	mg – miligramos
	ml – mililitros
	ul – microlitros
	MeCN - acetonitrilo
15	MeOH – metanol
	EtOH – etanol
	Et ₂ O – éter dietílico
	EtOAc – acetato de etilo
	DCM – diclorometano
20	DIAD – azodicarboxilato de diisopropilo
	DIPEA - N,N-diisopropiletilamina
	DMAP - N,N-dimetil-4-piridinamina
	DME – 1,2-bis(metiloxi) etano

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	DMF – N,N-dimetilformamida
	DMSO - dimetilsulfóxido
	EDAC – clorhidrato de N- (3- Dimetilaminopropil)- N'-etilcarbodiimida
5	EDC – clorhidrato de N-(3-Dimetilaminopropil)-N'-etilcarbodiimida
	EDCI – clorhidrato de N- (3- Dimetilaminopropil)- N'-etilcarbodiimida
	HOBT/HOBt – Hidroxibenzotriazol
	IPA- alcohol isopropílico
10	NCS – N-clorosuccinimida
	PyBOP – hexafluorofosfato de benzotriazol-1-il-oxitripirrolidin fosfonio
	THF – tetrahidrofurano
	dba – dibenciliden acetona
15	RT – temperatura ambiente
	°C – grados Celsius
	M – Molar
	H – protón
	s – singulete
20	d – doblete
	t – triplete
	q – cuartete
	MHz – megahertz

29

MeOD – metanol deuterado

LCMS – Espectrometría de Masas por Cromatografía de
Líquidos

LC/MS – Espectrometría de Masas por Cromatografía de

5 Líquidos

MS – espectrometría de masas

ES – electroaspersión

MH^+ – ion de masa + H^+

MDAP – cromatografía de líquidos preparativa automatizada

10 dirigida a masa

sat. – Saturado

Boc – ter-butiloxycarbonilo

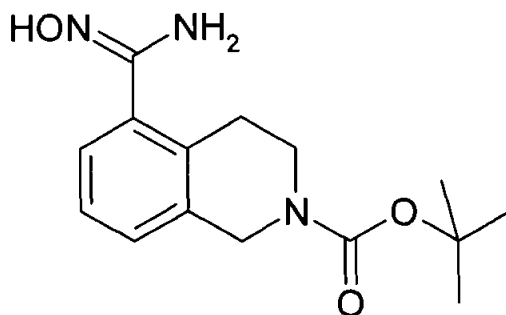
SCX o SCX-3 - columna de extracción en fase sólida (SPE) con
residuos de ácido bencensulfónico inmovilizados en la fase sólida (por
15 ejemplo, columnas IST IsoluteTM).

Sección de química general

Los métodos descritos a continuación se dan para propósitos
ilustrativos, los intermediarios en la preparación de los ejemplos pueden no
20 necesariamente haber sido preparados a partir de los lotes específicos
descritos.

Preparación 11,1-dimetiletil 5-[(hidroxiamino)(imino)metil]-3,4-dihidro-2(1H)-isoquinolincarboxilato

5



10 Clorhidrato de 1,2,3,4-tetrahidro-5-isoquinolincarbonitrilo (5.0 g/
25.7 mmoles, disponible de Fluorchem) fue dividido entre DCM (100 mL) y
NaOH 2N. La capa de DCM fue recolectada, secada (frita hidrofóbica) y
evaporada. La base libre, 1,2,3,4-tetrahidro-5-isoquinolincarbonitrilo fue
disuelta en DCM seco (100 mL) y tratada con dicarbonato de bis(1,1-
15 dimetiletilo) (1.1 equiv, 6.17 g). La reacción fue agitada a RT bajo argón
durante 18 horas, lavada con NaOH 2N (100 mL), HCl 2N (100 mL), secada
(frita hidrofóbica) y evaporada para dar el 1,1-dimetiletil-5-ciano-3,4-dihidro-
2(1H)-isoquinolincarboxilato crudo que se usó sin más purificación (LCMS
100%, RMN mezcla 2:1 con tBuOH). Rendimiento aislado 7.58 g. RMN ¹H
20 (400 MHz, CDCl₃) δ (entre otros) 7.52 (1H, d), 7.35-7.16 (2H, m), 4.60 (2H,
br.s), 3.71 (2H, t), 3.04 (2H, t), 1.5 (9H, s); m/z (API-ES) 203 [M+H-56]⁺.

El material crudo de arriba, hidroxilamina.HCl (14.31 g, 206
mmoles) y bicarbonato de sodio (21.63 g, 257 mmoles) fueron agregados a un

matraz de fondo redondo de 500 mL que contenía etanol (200 mL). La mezcla de reacción fue calentada a 65 °C durante 24 horas. La reacción enfriada fue evaporada y dividida entre DCM (2 x 100 mL) y agua (100 mL). Las capas de DCM combinadas fueron recolectadas y secadas. El análisis mediante LC/MS

5 mostró que el material es ~80% puro. El material fue disuelto en etanol (100 mL) y filtrado para retirar impurezas sin disolver. El análisis mediante LC/MS

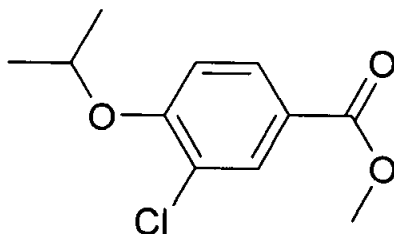
mostró que el material es ~92% puro. 1,1-dimetiletil 5-
[(hidroxiamino)(imino)metil]-3,4-dihidro-2(1H)-isoquinolincarboxilato fue usado sin más purificación. RMN ¹H (400 MHz, CDCl₃) δ 7.82 (1H, br.s), 7.36-7.16

10 (3H, m), 4.80 (2H, br.s), 4.58 (2H, br.s), 3.59 (2H, br.t), 2.98 (2H, t), 1.49 (9H, s); m/z (API-ES) 292 [M+H]⁺.

Preparación 2

3-cloro-4-[(1-metiletil)oxi]benzoato de metilo

15



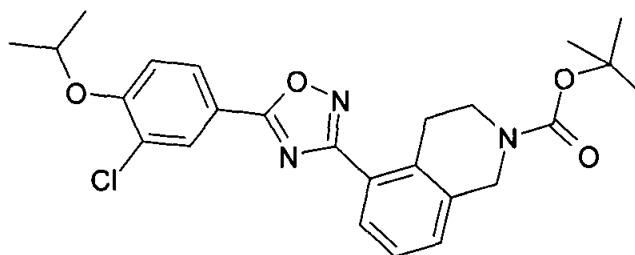
20

3-cloro-4-hidroxibenzoato de metilo (50 g, 0.27 moles), K₂CO₃ (74 g, 0.54 moles) y yodopropano (29.5 mL, 0.23 moles) fueron agitados a temperatura ambiente en DMF (100 mL). Después de 18 horas, el solvente

fue retirado por evaporación bajo vacío y el residuo fue sometido a cromatografía sobre una columna de sílice 60 en EtOAc/hexano (1:1) para dar el compuesto del título como un aceite (55 g, 90%). RMN ^1H (400 MHz, CDCl_3) δ 8.05 (1H, d), 7.89 (1H, dd), 6.94 (1H, d), 4.60-4.72 (1H, m), 3.89 (3H, s), 1.41 (6H, d); m/z (API-ES) 229 $[\text{M}+\text{H}]^+$.

Preparación 3

1,1-dimetiletil 5-(5-{3-cloro-4-[(1-metiletil)oxil]fenil}-1,2,4-oxadiazol-3-il)-3,4-dihidro-2(1H)-isoquinolincarboxilato



1,1-dimetiletil 5-[(hidroxiamino)(imino)metil]-3,4-dihidro-2(1H)-isoquinolin carboxilato (Preparación 1) (2 g, 6.86 mmoles) fue disuelto en tetrahidrofurano (THF) (100 mL) y agitado con hidruro de sodio (60% de dispersión, 0.302 g, 7.55 mmoles) bajo argón a temperatura ambiente durante 30 minutos. Luego 3-cloro-4-[(1-metiletil)oxil]benzoato de metilo (Preparación 2) (2.355 g, 10.30 mmoles) se agregó y la reacción se calentó a temperatura de reflujo durante 1.5 horas. La reacción enfriada fue evaporada y dividida entre DCM (100 mL) y agua (100 mL). La capa de agua fue lavada con DCM

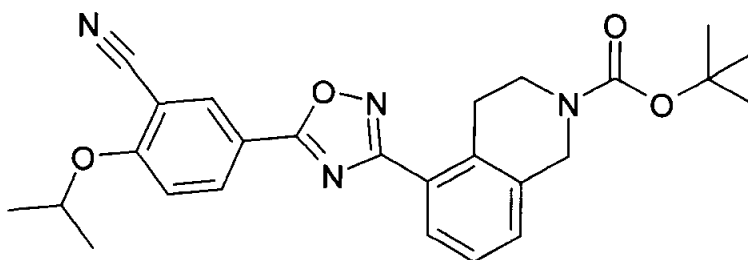
(50 mL) y las capas de DCM combinadas fueron secadas (frita hidrofóbica) y evaporadas. El producto crudo fue purificado mediante cromatografía mediante una pequeña almohadilla de sílice, eluyendo con de DCM para producir 1,1-dimetiletil 5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-3,4-dihidro-2(1H)-isoquinolin carboxilato (2.57 g, 5.47 mmoles, 80% rendimiento). RMN ^1H (400 MHz, CDCl_3) δ 8.23 (1H, s), 8.05 (1H, d), 7.95 (1H, d), 7.34 (1H, t), 7.27 (1H, d), 7.06 (1H, d), 4.76-4.63 (1H, m), 4.66 (2H, br.s), 3.67 (2H, br.t), 3.25 (2H, br.t), 1.51 (9H, s), 1.45 (6H, d); m/z (API-ES) 414, 416 $[\text{M}+\text{H}-56]^+$.

10

Preparación 4

1,1-dimetiletil 5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-3,4-dihidro-2(1H)-isoquinolincarboxilato

15



20

A una solución de ácido 3-ciano-4-[(1-metiletil)oxi]benzoico (se puede preparar como se describe en WO2005/58848, 737 mg, 3.59 mmoles) y cloruro de oxalilo (360 μl) en DCM (20 mL) se agregó DMF (20 μl). La solución fue agitada a temperatura ambiente durante 90 minutos, luego fue

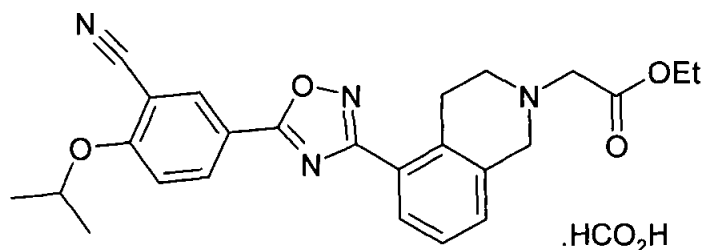
concentrada *in vacuo*, y redissuelta en DMF seco (6 mL). Por separado, 1,1-dimetiletil 5-[(hidroxiamino)(imino)metil]-3,4-dihidro-2(1H)-isoquinolin carboxilato (Preparación 1, 1.05 g, 3.60 mmoles), N,N-dimetil-4-piridinamina (DMAP) (20 mg) y N,N-diisopropiletilamina (DIPEA) (1.31 mL, 7.50 mmoles) se disolvieron en DMF (10 mL). 5 mL de la primera solución de DMF se agregaron a la segunda solución, y la solución amarilla fue agitada a temperatura ambiente durante 1 hora y luego a 95°C durante 18 horas. La reacción fue concentrada *in vacuo*, luego fue dividida entre DCM (50 mL) y NaHCO₃ saturado acuoso (50 mL). Las capas orgánicas fueron lavadas con NaHCO₃ saturado acuoso (50 mL), luego la capa acuosa combinada fue extraída con DCM (20 mL). Las capas orgánicas combinadas fueron concentradas *in vacuo* para dar un aceite café crudo. La cromatografía de columna rápida (gradiente [0.5-4%] MeOH en DCM) y concentración *in vacuo* dieron el compuesto del título como un sólido amarillo pálido (512 mg, 37%).

15 RMN ¹H (400 MHz, CDCl₃) δ 8.42 (1H, d), 8.34 (1H, dd), 7.96 (1H, d), 7.34 (1H, t), 7.29 (1H, d), 7.13 (1H, d), 4.80 (1H, sept), 4.67 (2H, s), 3.68 (2H, t), 3.24 (2H, t), 1.51 (9H, s), 1.48 (6H, d); m/z (ES) 361 [M+H-100]⁺.

Preparación 5

Sal de ácido fórmico de etil [5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-3,4-dihidro-2(1H)-isoquinolinil]acetato

5

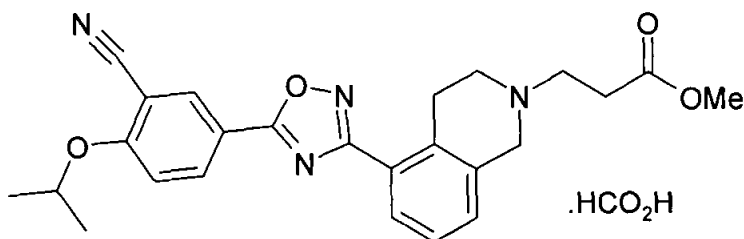


- 10 Una suspensión de 2-[(1-metiletil)oxi]-5-[3-(1,2,3,4-tetrahidro-5-isoquinolinil)-1,2,4-oxadiazol-5-il]benzonitrilo (Ejemplo 3, 28.8 mg, 0.080 mmoles), bromoacetato de etilo (35.5 μ l, 0.32 mmoles) y Cs_2CO_3 (130 mg, 0.40 mmoles) en DMF (2 mL) fue agitada a temperatura ambiente durante 1 hora, y luego irradiada a 60 $^{\circ}\text{C}$ durante 5 minutos en el horno de microondas.
- 15 La suspensión fue agregada a un cartucho SCX, y el producto fue eluido con amoníaco metanólico. La concentración *in vacuo* dio un producto crudo (43 mg) que fue purificado mediante MDAP para dar el compuesto del título como una película transparente (11.6 mg, 32 %). RMN ^1H (400 MHz, CDCl_3) δ 8.41 (1H, d), 8.33 (1H, dd), 8.09 (1H, br. s), 8.01 (1H, d), 7.34 (1H, aparente t), 7.21 (1H, d), 7.12 (1H, d), 4.80 (1H, sept), 4.24 (2H, q), 4.00 (2H, s), 3.52 (2H, s), 3.35 (2H, t), 3.07 (2H, t), 1.48 (6H, d), 1.31 (3H, t); m/z (ES) 447 $[\text{M}+\text{H}]^+$.
- 20

Preparación 6

Sal de ácido fórmico de metil 3-[5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-3,4-dihidro-2(1H)-isoquinolinil]propanoato

5



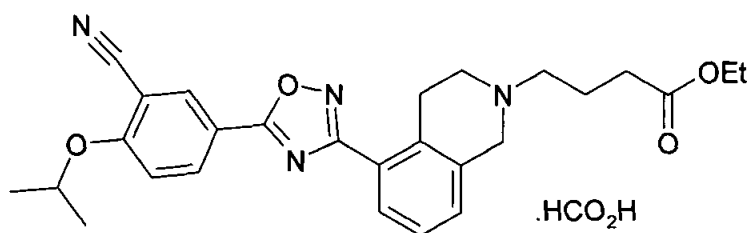
Una suspensión de 2-[(1-metiletil)oxi]-5-[3-(1,2,3,4-tetrahidro-5-isoquinolinil)-1,2,4-oxadiazol-5-il]benzonitrilo (Ejemplo 3, 28.8 mg, 0.080
10 mmoles), 3-bromopropionato de metilo (35 μ l, 0.32 mmoles) y Cs_2CO_3 (130 mg, 0.40 mmoles) en DMF (2 mL) fue agitada a temperatura ambiente durante 1 hora, y después irradiada a 60°C durante 5 minutos en el horno de microondas. Se añadió más 3-bromopropionato de metilo (35 μ l, 0.32 mmoles)
15 y la suspensión fue agitada a temperatura ambiente durante 3.5 horas, y luego fue irradiada a temperaturas crecientes en el horno de microondas hasta que se llegó a 150°C durante 30 minutos. La suspensión fue filtrada y concentrada *in vacuo*, luego purificada por MDAP para dar el compuesto del título como una película amarilla (5.9 mg, 17%). RMN ^1H (400 MHz, CDCl_3) δ 8.42 (1H, d),
20 8.33 (1H, dd), 8.21 (1H, br. s), 8.04 (1H, d), 7.35 (1H, t), 7.24 (1H, d), 7.13 (1H, d), 4.80 (1H, sept), 3.99 (2H, s), 3.72 (3H, s), 3.38 (2H, t), 3.12-3.06 (4H, m), 2.78 (2H, t), 1.48 (6H, d); m/z (ES) 447 $[\text{M}+\text{H}]^+$.

CP

Preparación 7

Sal de ácido fórmico de etil 4-[5-(5-[3-ciano-4-[(1-metiletil)oxi]fenil]-1,2,4-oxadiazol-3-il)-3,4-dihidro-2(1H)-isoquinolinil]butanoato

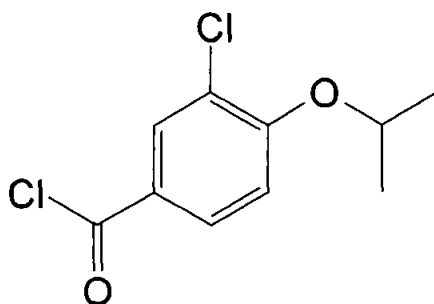
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Una suspensión de 2-[(1-metiletil)oxi]-5-[3-(1,2,3,4-tetrahidro-5-isoquinolinil)-1,2,4-oxadiazol-5-il]benzonitrilo (Ejemplo 3, 28.8 mg, 0.080 mmoles), 4-bromobutirato de etilo (45.8 μ l, 0.32 mmoles) y Cs_2CO_3 (130 mg, 0.40 mmoles) en DMF (2 mL) fue agitada a temperatura ambiente durante 1 hora, y después irradiada a 60°C durante 5 minutos en el horno de microondas. Se añadió más 4-bromobutirato de etilo (45.8 μ l, 0.32 mmoles) y la suspensión fue agitada a temperatura ambiente durante 3.5 horas. Después fue filtrada, concentrada *in vacuo* y purificada mediante MDAP para dar el compuesto del título como una película amarilla (8.0 mg, 21%). RMN ^1H (400 MHz, CDCl_3) δ 8.42 (1H, d), 8.34 (1H, dd), 8.27 (br. s), 8.09 (1H, d), 7.39 (1H, t), 7.27 (1H, d), 7.13 (1H, d), 4.80 (1H, sept), 4.19 (2H, s), 4.13 (2H, q), 3.47 (2H, t), 3.28 (2H, t), 2.99 (2H, t), 2.44 (2H, t), 2.10 (2H, quin), 1.48 (6H, d), 1.25 (3H, t); m/z (ES) 475 $[\text{M}+\text{H}]^+$.

Preparación 8Cloruro de 3-cloro-4-[(1-metiletil)oxil]benzoilo

5



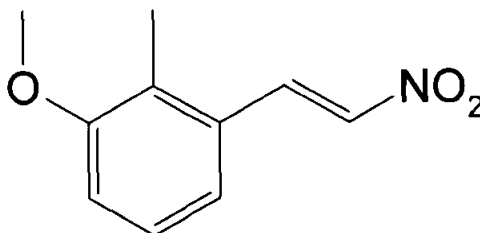
Un matraz de fondo redondo fue cargado con ácido 3-cloro-4-[(1-
10 metiletil)oxil]benzoico (disponible de la Lista de Productos Paragos, 10.2 g,
47.5 mmoles), diclorometano (158 ml) y cloruro de oxalilo (8.29 ml, 95
mmoles). La mezcla de reacción fue enfriado a 0°C en un baño de hielo/agua
antes de la adición de N,N-dimetilformamida (0.158 ml). La solución se dejó
calentar a temperatura ambiente toda la noche. El solvente fue evaporado
15 para producir el compuesto del título como un sólido color crema (11.4 g).

RMN ¹H (CLOROFORMO-d) δ: 8.14 (d, 1H), 8.00 (dd, 2.5 Hz,
1H), 6.98 (d, 1H), 4.73 (spt, 1H), 1.44 (d, 6H)

20

Preparación 92-Metil-1-(metiloxi)-3-[(E)-2-nitroetenil]benceno

5



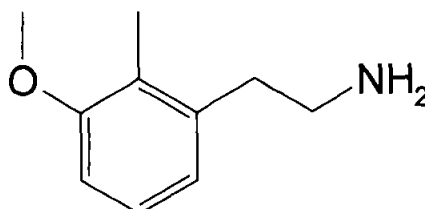
A una solución de 2-metil-3-(metiloxi)benzaldehído (disponible de
10 la Lista de Productos Allichem; 20 g; 133 mmoles) en nitrometano (400 ml) se
añadió acetato de amonio (6.16 g; 80 mmoles) y la mezcla naranja resultante
fue agitada durante 1 hora a 100°C, luego enfriada a temperatura ambiente y
concentrada *in vacuo*. El residuo fue dividido entre acetato de etilo (x2) y
salmuera, y las capas orgánicas fueron lavadas con salmuera, secadas
15 (MgSO₄) y concentradas *in vacuo*. La trituración con diclorometano/éter dio el
compuesto del título como un sólido amarillo (6.6 g).

RMN ¹H (CDCl₃) δ: 8.35 (d, 1H), 7.48 (d, 1H), 7.22 (t, 1H), 7.11
(d, 1H), 6.96 (d, 1H), 3.86 (s, 3H), 2.33 (s, 3H)

Después de la evaporación de las soluciones madre se obtuvo
20 más producto (7.22 g) mediante trituración con éter dietílico. Las soluciones
madre fueron de nuevo evaporadas y el residuo fue purificado mediante
cromatografía, eluyendo con 5-10% acetato de etilo en ciclohexano, para dar
más producto (3.45 g) después de trituración con éter.

Preparación 10{2-[2-Metil-3-(metiloxi)fenil]etil}amina

5



A borohidruro de litio (2M en THF; 2.0 ml; 4.0 mmoles) (turbio) a
10 temperatura ambiente se añadió gota a gota durante 0.5 minutos
clorotrimetilsilano (1.02 ml; 8.00 mmoles). Se formó un precipitado y después
de aproximadamente 3 minutos, 2-metil-1-(metiloxi)-3-[(E)-2-nitroetenil]
benceno (Preparación 9, 193 mg; 1.0 mmoles) en THF (4 ml) se añadió gota a
gota vía una jeringa durante 5 minutos, asegurando que la temperatura
15 permaneciera a aproximadamente 25°C (usando un baño frío de agua). La
solución fue agitada a temperatura ambiente toda la noche. La mezcla fue
enfriada con un baño de hielo, se añadió metanol lentamente y el solvente fue
retirado *in vacuo*. El residuo fue dividido entre 25% hidróxido de sodio acuoso
y diclorometano. La fase acuosa fue separada y extraída tres veces con
20 diclorometano y las capas orgánicas combinadas fueron evaporadas. La
purificación del residuo mediante extracción en fase sólida (columna SCX),
eluyendo con metanol seguido de amoníaco 2N en metanol, seguido de

evaporación de la fracción que contiene amoníaco dio el compuesto del título (80 mg).

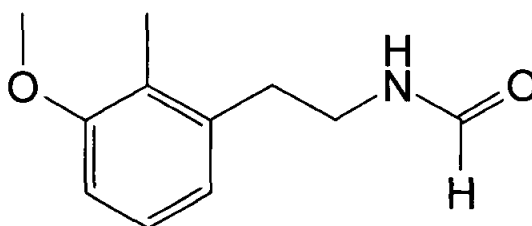
RMN ^1H (CDCl_3) δ : 7.10 (t, 1H), 6.78 (d, 1H), 6.73 (d, 1H), 3.81 (s, 3H), 2.91 (t, 2H), 2.77 (t, 2H), 2.18 (s, 3H), 1.76 (br. s., 2H)

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Preparación 11

{2-[2-Metil-3-(metiloxi)fenil]etil}formamida

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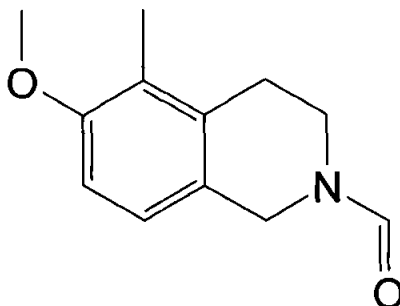
{2-[2-Metil-3-(metiloxi)fenil]etil}amina (Preparación 10; 1.75 g; 10.6 mmoles) fue calentada bajo reflujo con formiato de etilo (97%; 15 ml) durante 15 horas. La remoción del solvente dio el producto crudo (aproximadamente 2 g), el cual fue purificado mediante cromatografía en gel de sílice, eluyendo con un gradiente de 13-63% acetato de etilo en ciclohexano, para dar el compuesto del título (1.57 g).

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MS m/z 194 [MH^+]

Preparación 125-Metil-6-(metiloxi)-3,4-dihidro-2(1H)-isoquinolincarbaldhído

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A una solución de {2-[2-metil-3-(metiloxi)fenil]etil}formamida (Preparación 11; 1.93 g; 10.0 mmoles) en ácido fórmico (20 ml) se añadió paraformaldehído (0.315 g; 10.5 mmoles) y la mezcla resultante fue calentada bajo reflujo (100 °C) durante 20 minutos.

15

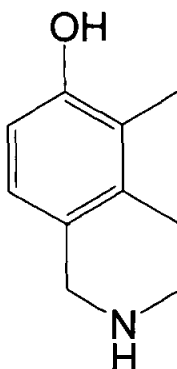
La mezcla fue enfriada rápidamente a temperatura ambiente con agua enfriada con hielo, y el solvente fue retirado. La purificación mediante cromatografía en gel de sílice, eluyendo con un gradiente de metanol en diclorometano, dio el compuesto del título como un sólido blanco (1.64 g), el cual se usó sin más purificación.

MS m/z 206 [MH⁺]

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Preparación 135-Metil-1,2,3,4-tetrahidro-6-isoquinolinol

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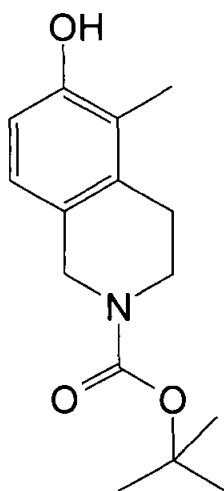
10 A una solución de 5-metil-6-(metiloxi)-3,4-dihidro-2(1H)-
isoquinolincarbaldéido (Preparación 12; 1.49 g; 7.26 mmoles) en
diclorometano (25 ml) a 0°C bajo nitrógeno se añadió lentamente tribromuro
de boro (9.09 g; 36.3 mmoles). Después de 85 minutos a 0°C, metanol (25 ml)
se agregó lentamente, y la mezcla resultante se dejó reposar a temperatura
15 ambiente por tres días. La remoción del solvente y trituración con
metanol/diclorometano dieron un residuo sólido blanco; las soluciones madre
fueron concentradas y el residuo aplicado a un cartucho de extracción en fase
sólida SCX (20 g) y eluído con metanol seguido de amoníaco 2N en metanol
para eluir el producto. Después de evaporación del solvente el compuesto del
20 título (780 mg) se obtuvo como un sólido amarillo pálido.

RMN ^1H (DMSO- d_6) δ : 8.91 (br. s., 1H), 6.62 (d, 1H), 6.56 (d,
1H), 3.70 (s, 2H), 2.92 (t, 2H), 2.48 (t, 2H), 1.96 (s, 3H)

Preparación 141,1-Dimetiletil 6-hidroxi-5-metil- 3,4-dihidro-2(1H) -isoquinolincarboxilato

5

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A una suspensión de 5-metil-1,2,3,4-tetrahidro-6-isoquinolinol (Preparación 13; 163 mg; 1.0 mmoles) en diclorometano (5 ml) a 0°C se
15 añadió trietilamina (0.21 ml; 1.50 mmoles) seguido de dicarbonato de bis(1,1-dimetiletilo) (240 mg; 1.10 mmoles).

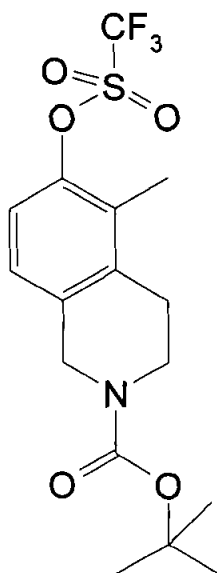
El solvente fue evaporado y el residuo dividido entre acetato de etilo y salmuera. La capa acuosa fue extraída aún más con acetato de etilo y las capas orgánicas combinadas fueron secadas (MgSO₄) y evaporadas para
20 dar un aceite amarillo. La purificación mediante cromatografía de columna rápida eluyendo con un gradiente de 5-25% acetato de etilo en ciclohexano dio el compuesto del título como una espuma blanca (232 mg).

MS m/z 262 [M-H]

Preparación 151,1-Dimetiletil 5-metil-6-[(trifluorometil)sulfonil]oxi}-3,4-dihidro-2(1H)-isoquinolincarboxilato

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A una solución de 1,1-dimetiletil 6-hidroxi-5-metil-3,4-dihidro-2(1H)-isoquinolincarboxilato (Preparación 14; 263 mg; 1.00 mmoles) en diclorometano (5 ml) a -30°C bajo nitrógeno se agregó piridina (0.162 ml; 2.00 mmoles) seguido de adición lenta de anhídrido trifluorometansulfónico (0.186 ml; 1.10 mmoles). Después de 0.5 horas entre -30°C y -20°C, el solvente fue retirado, y el residuo absorbido en acetato de etilo. La solución fue lavada con ácido clorhídrico 1N seguido de solución saturada de bicarbonato de sodio, secada (MgSO₄) y concentrada *in vacuo* para dar el compuesto del título como un aceite amarillo pálido (368 mg).

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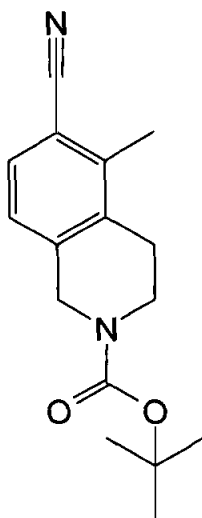
MS m/z 394 [M-H]

Preparación 16

1,1-Dimetiletil 6-ciano-5-metil-3,4-dihidro-2(1H)-isoquinolin

5 carboxilato

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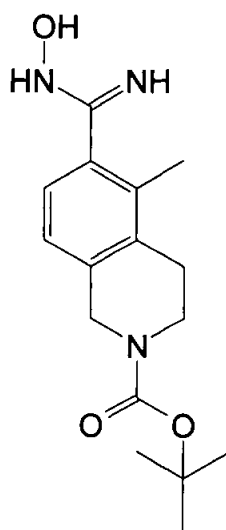
Una solución de 1,1-dimetiletil 5-metil-6-[[trifluorometil]sulfonil]oxi-3,4-dihidro-2(1H)-isoquinolincarboxilato (Preparación 15; 395 mg; 1.00 mmoles) en DMF (4 ml) fue degasificada bajo alto vacío con agitación durante 15 minutos, seguido de adición de cianuro de zinc (153 mg; 1.30 mmoles) y tetrakis(trifenilfosfin)paladio (0) (116 mg; 0.10 mmoles) bajo nitrógeno. La mezcla amarillo oscuro resultante fue agitada a 100°C durante 6 horas. El solvente fue retirado, el residuo fue disuelto en acetato de etilo, y la solución fue lavada con bicarbonato de sodio saturado. La capa acuosa fue extraída

aún más con acetato de etilo, y las capas orgánicas combinadas fueron lavadas con salmuera, secadas (MgSO_4), y evaporadas para dar el producto crudo. La purificación mediante cromatografía de columna rápida en gel de sílice, eluyendo con un gradiente de 5-25% acetato de etilo en ciclohexano, dio el compuesto del título (214 mg) como un sólido blanco.

RMN ^1H (CDCl_3) δ : 7.44 (d, 1H), 7.04 (d, 1H), 4.60 (s, 2H), 3.69 (t, 2H), 2.75 (t, 2H), 2.46 (s, 3H), 1.49 (s, 9H)

Preparación 17

1,1-Dimetiletil 6-[(hidroxiamino)(imino)metil]-5-metil-3,4-dihidro-2(1H)-isoquinolincarboxilato



1,1-Dimetiletil 6-ciano-5-metil- 3,4-dihidro-2(1H)- isoquinolin carboxilato (Preparación 16; 404 mg; 1.48 mmoles) se agitó toda la noche a

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80 °C con clorhidrato de hidroxilamina (619 mg; 8.90 mmoles) y bicarbonato de sodio (748 mg; 8.9 mmoles) en etanol (10 ml). Se añadieron más bicarbonato de sodio (400 mg) y clorhidrato de hidroxilamina (300 mg), y el calentamiento continuó durante aproximadamente 8 horas. La mezcla fue
5 enfriada a temperatura ambiente, y el sólido resultante fue removido, lavado con etanol, y secado bajo alto vacío para dar el compuesto del título como un sólido blanco (431 mg).

RMN ¹H (DMSO-d₆) δ: 7.06 (d, 1H), 6.99 (d, 1H), 4.48 (br. s., 2H), 3.58 (t, 2H), 2.67 (t, 2H), 2.19 (s, 3H), 1.42 (s, 9H) (los elementos
10 intercambiables no están listados; no se observaron claramente).

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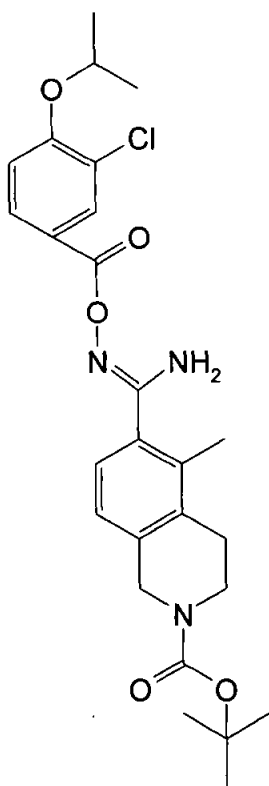
Preparación 18

1,1-Dimetiletil 6-[[[(3-cloro-4-[(1-metiletil)oxi]fenil)carbonil)oxi]amino](imino)metil]-5-metil-3,4-dihidro-2(1H)-isoquinolincarboxilato

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A una solución de 1,1-dimetiletil 6-[(hidroxiamino)(imino)metil]-5-metil-3,4-dihidro-2(1H)-isoquinolincarboxilato (Preparación 17; 435 mg; 1.42 mmoles) en diclorometano (10 ml) se añadió trietilamina (0.30 ml; 2.14 mmoles) seguido de cloruro de 3-cloro-4-[(1-metiletil)oxi]benzoilo (Preparación 8; 365 mg; 1.57 mmoles) en diclorometano (5 ml). Después de 30 minutos, la reacción fue concentrada, y el residuo dividido entre acetato de etilo y bicarbonato de sodio saturado. La capa acuosa fue extraída aún más con

acetato de etilo, y las capas orgánicas combinadas fueron lavadas con salmuera, secadas (MgSO_4) y concentradas *in vacuo*. La purificación mediante cromatografía de columna rápida en gel de sílice, eluyendo con un gradiente de 10-50% acetato de etilo en ciclohexano dio el compuesto del

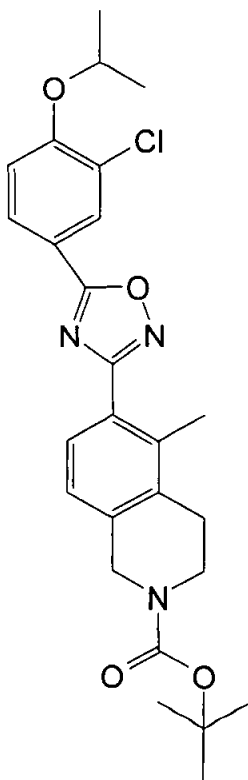
5 título como una espuma blanca (413 mg).

MS m/z 500 [M-H]

Preparación 19

1,1-Dimetiletil 6-(5-{3-cloro- 4-[(1-metiletil)oxi] fenil}-1,2,4-

10 oxadiazol-3-il)-5-metil-3,4-dihidro-2(1H)-isoquinolincarboxilato



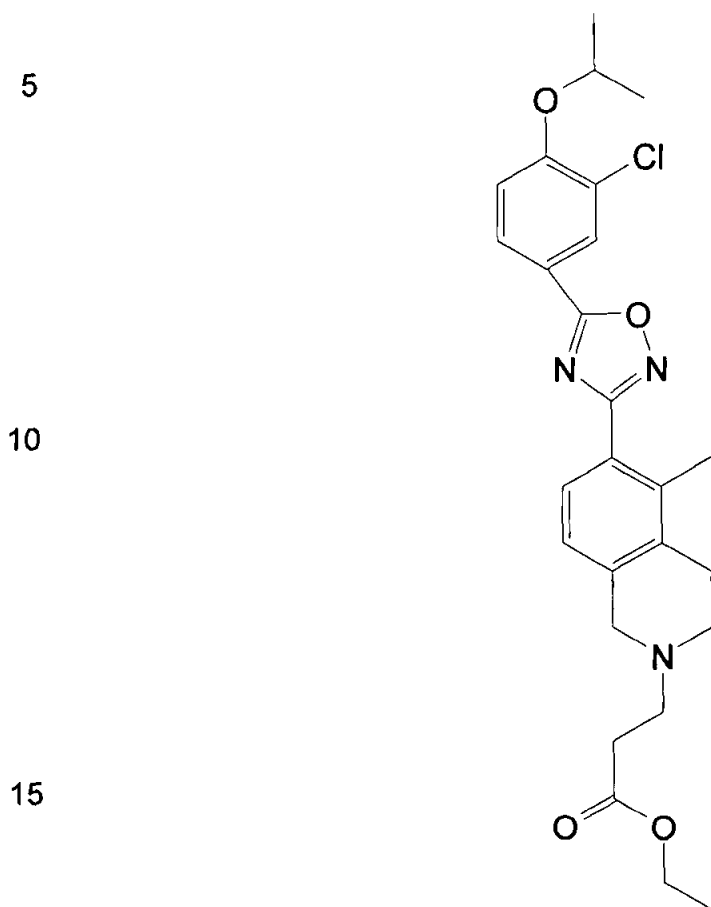
///

Una solución de 1,1-dimetiletil 6-[[[({3-cloro-4-[(1-metiletil)oxi]fenil}carbonil)oxi] amino}(imino)metil]- 5-metil-3,4-dihidro-2(1H)-isoquinolin carboxilato (Preparación 18; 413 mg; 0.823 mmoles) en 1,4-dioxano (15 ml) fue agitada a 110°C durante aproximadamente 18 horas. La mezcla fue
5 enfriada a temperatura ambiente y el solvente fue retirado. La purificación mediante cromatografía de columna rápida en gel de sílice, eluyendo con 5-25% acetato de etilo en ciclohexano seguido de 13-63% acetato de etilo en ciclohexano, dio el compuesto del título como una espuma blanca (220 mg).

RMN ¹H (CLOROFORMO-d) δ: 8.24 (d, 1H), 8.05 (dd, 1H), 7.76
10 (d, 1H), 7.10 (d, 1H), 7.06 (d, 1H), 4.72 (spt, 1H), 4.63 (s, 2H), 3.71 (t, 2H), 2.84 (t, 2H), 2.52 (s, 3H), 1.51 (s, 9H), 1.45 (d, 6H)

Preparación 20

Etil 3-[6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-5-metil-3,4-dihidro-2(1H)-isoquinolinil]propanoato



A una suspensión de trifluoroacetato de 6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}- 1,2,4-oxadiazol-3-il)-5- metil-1,2,3,4-tetrahidroisoquinolina
20 (Ejemplo 10; 90 mg; 0.18 mmoles) en acetonitrilo (3 ml) se agregó 1,8-diazabicyclo[5.4.0]undec-7-eno (DBU; 0.16 ml; 1.09 mmoles). Acrilato de etilo (0.03 ml; 0.27 mmoles) se agregó a la solución y la mezcla resultante se agitó a 70°C durante 0.5 horas. La mezcla fue enfriada a temperatura ambiente y el

solvente fue retirado. El residuo fue dividido entre acetato de etilo y salmuera, y la capa acuosa fue extraída aún más con acetato de etilo. Las capas orgánicas combinadas fueron lavadas con salmuera, secadas (MgSO_4) y concentradas *in vacuo* para dar el compuesto del título (90 mg).

5 MS m/z 484 [MH^+]

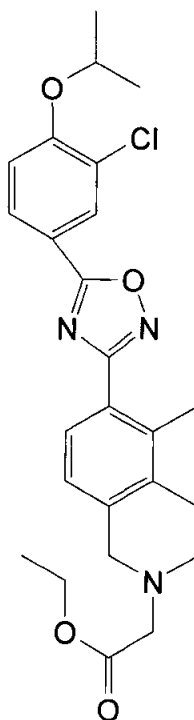
Preparación 21

Etil [6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-5-metil-3,4-dihidro-2(1H)-isoquinolinil]acetato

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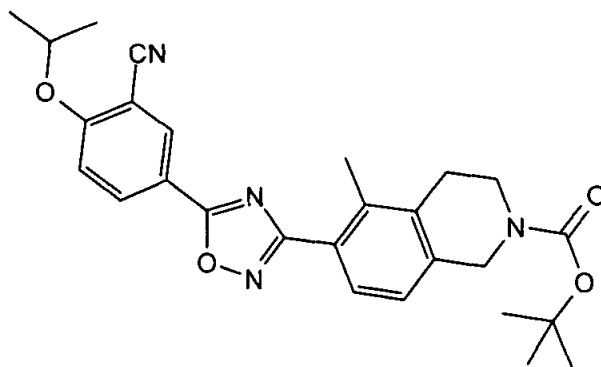
A una suspensión de trifluoroacetato de 6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-5-metil-1,2,3,4-tetrahidroisoquinolina (Ejemplo 10; 90 mg; 0.18 mmoles) en DMF (3 ml) bajo nitrógeno a temperatura ambiente se agregó carbonato de cesio (177 mg; 0.54 mmoles) seguido de bromoacetato de etilo (0.026 ml; 0.23 mmoles). Después de 35 minutos, la mezcla fue diluida con acetato de etilo y el precipitado fue retirado. La solución fue lavada con agua y la capa acuosa fue extraída aún más con acetato de etilo. La capa orgánica fue lavada con salmuera, secada sobre MgSO_4 y concentrada *in vacuo* para dar el compuesto del título (75 mg).

10 MS m/z 470 $[\text{MH}^+]$

Preparación 22

1,1-Dimetiletil 6-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-5-metil-3,4-dihidro-2(1H)-isoquinolincarboxilato

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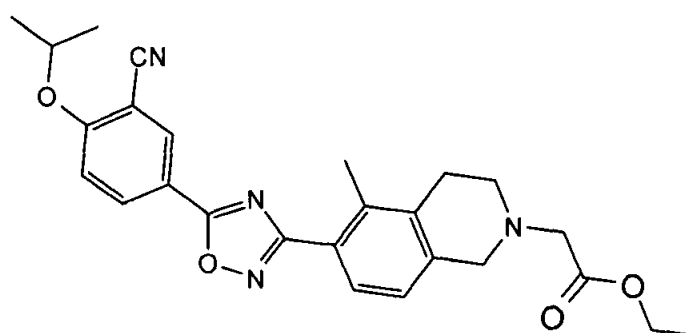
Cloruro de oxalilo (571 mg, 4.5 mmoles) se añadió a una solución de ácido 3-ciano-4-[(1-metiletil)oxi]benzoico (disponible del Catálogo de productos AK Scientific; 800 mg, 3.90 mmoles) en diclorometano (15 ml) seguido de DMF (cantidad catalítica). La mezcla de reacción se agitó durante 5 45 minutos, se agregaron más cloruro de oxalilo (0.1 ml) y DMF (1 gota) y la agitación continuó durante 20 minutos. El solvente fue evaporado, el residuo fue co-evaporado con tolueno y después secado bajo alto vacío durante 30 minutos. El cloruro de ácido crudo fue disuelto en acetonitrilo (10 ml) y agregado a una suspensión de 1,1-dimetiletil 6-[(hidroxiamino)(imino)metil]-5-10 metil-3,4-dihidro-2(1H)-isoquinolincarboxilato (Preparación 17; 916 mg, 3.00 mmoles) y trietilamina (607 mg, 6.00 mmoles) en acetonitrilo (15 ml). La mezcla de reacción fue agitada a temperatura ambiente durante 40 minutos, después calentada bajo reflujo durante 24 horas. La mezcla de reacción fue enfriada y el solvente fue evaporado. El residuo fue dividido entre acetato de 15 etilo y solución saturada de bicarbonato de sodio. La fase orgánica fue separada, lavada con salmuera, secada (MgSO_4) y evaporada para dar el producto crudo (1.3 g). El residuo fue purificado mediante cromatografía, eluyendo con 8-38% acetato de etilo en ciclohexano, para dar el compuesto del título (486 mg).

20 RMN ^1H (CLOROFORMO- d) δ : 8.42 (d, 1H), 8.33 (dd, 1H), 7.76 (d, 1H), 7.12 (d, 1H), 7.11 (d, 1H), 4.80 (spt, 1H), 4.64 (s, 2H), 3.72 (t, 2H), 2.84 (t, 2H), 2.52 (s, 3H), 1.51 (s, 9H), 1.48 (d, 6H)

Preparación 23

Etil [6-(5-{3-ciano-4-[(1-metiletil)oxil]fenil}-1,2,4-oxadiazol-3-il)-5-metil-3,4-dihidro-2(1H)-isoquinolinil]acetato

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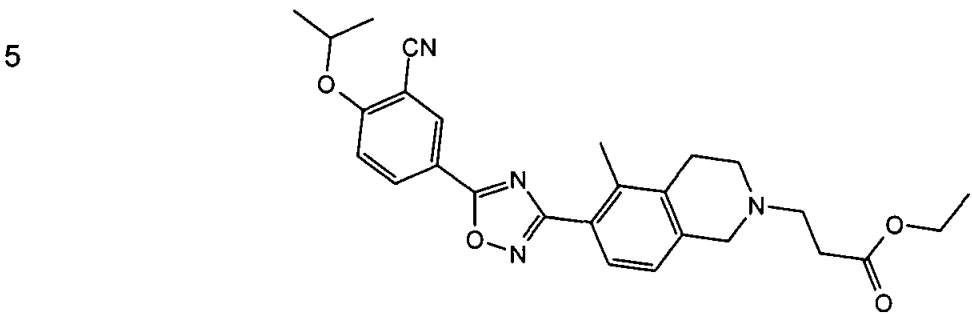


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Una mezcla de sal de ácido 2-[(1-metiletil)oxi]-5-[3-(5-metil-1,2,3,4-tetrahidro-6-isoquinolinil)-1,2,4-oxadiazol-5-il]benzonitril trifluoroacético (Ejemplo 11; 100 mg, 0.20 mmoles), bromoacetato de etilo (44 mg, 30 μ l, 0.26 mmoles) y carbonato de cesio (200 mg, 0.61 mmoles) en DMF seco (3 ml) se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción fue diluida con agua (10 ml) y extraída con acetato de etilo (3x5 ml). Los extractos combinados fueron sacados y evaporados. La purificación mediante cromatografía en gel de sílice, eluyendo con 10% acetato de etilo en ciclohexano dio el compuesto del título como un aceite incoloro (85 mg). MS m/z 461 $[MH]^+$.

Preparación 24

Etil 3-[6-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-5-metil-3,4-dihidro-2(1H)-isoquinolinil]propanoato

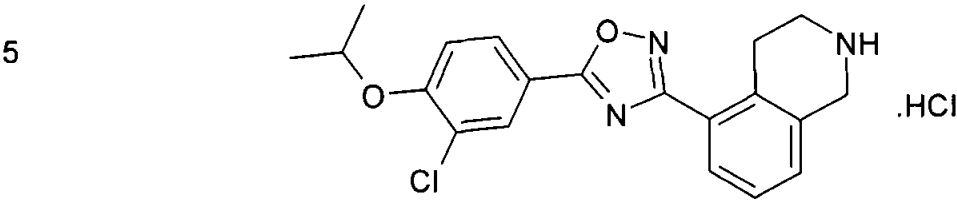


10 Una mezcla de sal de ácido 2-[(1-metiletil)oxi]-5-[3-(5-metil-1,2,3,4-tetrahidro-6-isoquinolinil)-1,2,4-oxadiazol-5-il]benzonitril trifluoroacético (Ejemplo 11; 100 mg, 0.20 mmoles), acrilato de etilo (31 mg, 33 µl, 0.31 mmoles) y 1,8-diazabicyclo[5.4.0]undec-7-eno (DBU; 187 mg, 185 µl, 1.23 mmoles) en acetonitrilo (3 ml) se agitó a temperatura ambiente durante 3

15 horas. El solvente fue evaporado y el residuo fue disuelto en acetato de etilo (10 ml); la solución fue lavada con agua (5 ml), secada y evaporada. La purificación del residuo mediante cromatografía en gel de sílice, eluyendo con 10% acetato de etilo en ciclohexano dio el compuesto del título como un aceite incoloro (86 mg). MS m/z 475 [MH]⁺.

EJEMPLO 1

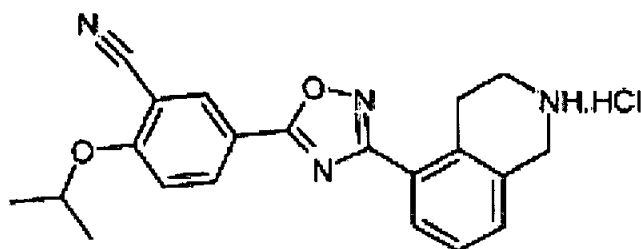
Clorhidrato de 5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,3,4-tetrahidroisoquinolina



1,1-dimetiletil 5-(5-{3-cloro-4- [(1-metiletil)oxi]fenil}- 1,2,4-
10 oxadiazol-3-il)-3,4-dihidro-2(1H)-isoquinolincarboxilato (Preparación 3) (2.57 g,
5.47 mmoles) se agitó en HCl 4M en 1,4-Dioxano (100 mL). Después de 1
hora de reacción se puso turbio y la agitación continuó durante otras 16 horas.
La evaporación produjo clorhidrato de 5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-
1,2,4-oxadiazol-3-il)-1,2,3,4-tetrahidroisoquinolina (2.23 g, 5.49 mmoles, 100%
15 rendimiento). RMN ¹H (400 MHz, d₆-DMSO) δ 9.43 (2H, s), 8.19 (1H, s), 8.11
(1H dd), 8.03-8.00 (1H, m), 7.51-7.45 (3H, m), 4.89 (1H, sept.), 4.38 (2H, s),
3.43 (2H, t), 3.35-3.32 (2H, m), 1.37 (6H, d); m/z (API-ES) 370, 372 [M+H]⁺.

EJEMPLO 2**Clorhidrato de 2-[(1-metiletil)oxi]-5-[3-(1,2,3,4-tetrahidro-5-isoquinolinil)-1,2,4-oxadiazol-5-il]benzonitrilo**

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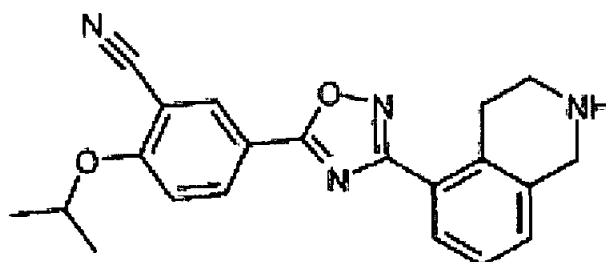


Una mezcla de 1,1-dimetiletil 5-(5-{3-ciano-4-[(1-metiletil)oxi]
10 fenil}-1,2,4-oxadiazol-3-il)-3,4-dihidro-2(1H)-isoquinolincarboxilato
(Preparación 4; 53.7 mg, 0.117 mmoles) y HCl 4M en dioxano (2 ml) se agitó a
temperatura ambiente durante 64 horas. La mezcla fue concentrada *in vacuo*,
el residuo fue triturado con Et₂O y secado *in vacuo* para dejar un sólido café
claro (35.1 mg, 76%). RMN ¹H (400 MHz, d₆-DMSO) δ 9.52 (2H, br. s), 8.52
15 (1H, d), 8.40 (1H, dd), 8.02 (1H, dd), 7.57, (1H, d), 7.51-7.48 (2H, m), 4.99
(1H, sept.), 4.38 (2H, s), 3.39-3.34 (4H, m), 1.39 (6H, d); m/z (ES) 361 [M+H]⁺.

20

EJEMPLO 3**2-[(1-metiletil)oxi]-5-[3-(1,2,3,4-tetrahidro-5-isoquinolinil)-1,2,4-oxadiazol-5-il]benzonitrilo**

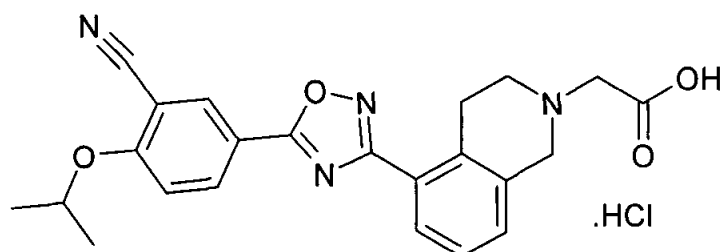
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- 10 Una mezcla de 1,1-dimetiletil 5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-3,4-dihidro-2(1H)-isoquinolincarboxilato (Preparación 4, 512 mg, 1.11 mmoles) y HCl 4M en dioxano (20 ml) fue agitada a temperatura ambiente durante 18 horas. La mezcla fue concentrada *in vacuo* para dar un sólido amarillo pálido, el cual fue redissuelto en MeOH.
- 15 Esta solución fue aplicada a un cartucho SCX-3 (10 g), y el producto fue eluído con 1% NH₃ en MeOH. La concentración dio un aceite amarillo, que se volvió un sólido en el reposo durante toda la noche (366 mg, 91%). RMN ¹H (400 MHz, d₆-DMSO) δ 8.38 (1H, d), 8.32 (1H, dd), 7.94 (1H, d), 7.32-7.17 (2H, m), 7.13 (1H, m), 4.80 (1H, sept), 4.10 (2H, s), 3.20-3.14 (4H, m), 1.48
- 20 (6H, d); m/z (ES) 361 [M+H]⁺.

EJEMPLO 4**Clorhidrato de ácido [5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-3,4-dihidro-2(1H)-isoquinolinil]acético**

5



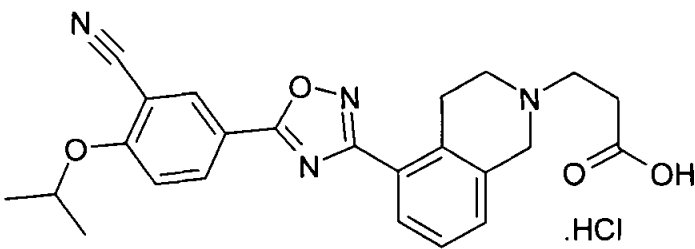
Una solución de sal de ácido fórmico de etil [5-(5-{3-ciano-4-[(1-
 10 metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-3,4-dihidro-2(1H)-isoquinolinil] acetato
 (Preparación 5, 11.6 mg, 0.026 mmoles) y LiOH (0.3 mg) en THF-MeOH-agua
 (300 μ l, 300 μ l, 200 μ L) fue irradiada a 100°C durante 3 minutos en el horno
 de microondas. Se añadió HCl acuoso 2M (1 mL), luego la solución fue
 extraída con DCM (2 x 2 mL). Las capas orgánicas combinadas fueron
 15 concentradas *in vacuo* para dar el compuesto del título como un sólido blanco
 (10.1 mg, 85 %). RMN ^1H (400 MHz, $\text{d}_4\text{-MeOH}$) δ 8.48 (1H, d), 8.44 (1H, dd),
 8.21 (1H, d), 7.44 (1H, t), 7.47 (2H, aparente d), 4.97 (1H, sept), 4.70 (2H, s),
 4.32 (2H, s), 3.67 (2H, t), 3.57 (2H, t), 1.47 (6H, d); m/z (ES) 419 $[\text{M}+\text{H}]^+$.

20

EJEMPLO 5

Clorhidrato de ácido 3-[5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-3,4-dihidro-2(1H)-isoquinolinil]propanoico

5

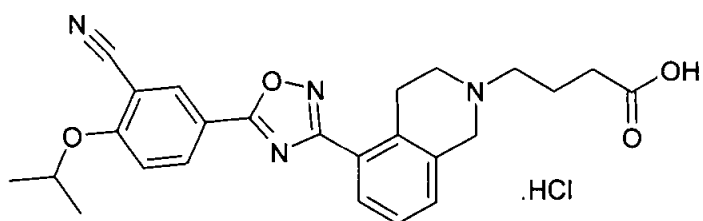


Una solución de sal de ácido fórmico de metil 3-[5-(5-{3-ciano-4-
10 [(1-metiletil)oxi]fenil}- 1,2,4-oxadiazol-3-il)-3,4- dihidro-2(1H)-isoquinolinil]
propanoato (Preparación 6, 5.9 mg, 0.0132 mmoles) y LiOH (0.15 mg) en
THF-MeOH-agua (300 µl, 300 µl, 100 µl) fue irradiada a 100°C durante 3
minutos en el horno de microondas. HCl acuoso 2M (1 ml) y DCM (2 ml) se
agregaron consecutivamente, y se formó un precipitado. La filtración dio el
15 compuesto del título como un sólido blanco (6.5 mg, cuant.). RMN ¹H (400
MHz, d₆-DMSO) δ 12.71 (1H, br s), 11.41 (1H, br s), 8.53 (1H, d), 8.41 (1H,
dd), 8.05 (1H, d), 7.57 (1H, d), 7.53 (1H, t), 7.46 (1H, d), 4.99 (1H, sept), 4.53
(2H, br s), 3.46-3.43 (4H, m), 3.65 (2H, br s), 2.98 (2H, t), 1.39 (6H, d); m/z
(ES) 433 [M+H]⁺.

20

EJEMPLO 6**Clorhidrato de ácido 4-[5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-3,4-dihidro-2(1H)-isoquinolinil]butanoico**

5

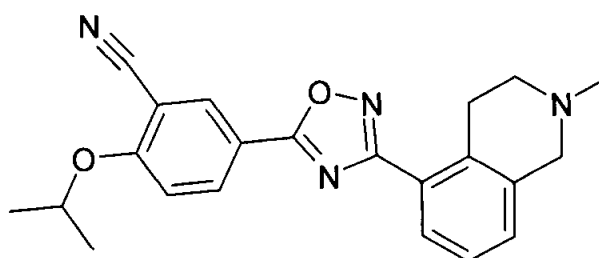


El compuesto del título se hizo de manera similar al Ejemplo 4,
 10 reemplazando etil [5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-
 3,4-dihidro-2(1H)-isoquinolinil]acetato con sal de ácido fórmico de etil 4-[5-(5-
 {3-ciano-4- [(1-metiletil)oxi]fenil}-1,2,4- oxadiazol-3-il)-3,4- dihidro-2(1H)-
 isoquinolinil]butanoato (Preparación 7, 8.0 mg). El compuesto del título se
 obtuvo como un sólido blanco (10.1 mg). RMN ^1H (400 MHz, $\text{d}_4\text{-MeOH}$) δ 8.36
 15 (1H, d), 8.33 (1H, dd), 8.23 (1H, d), 7.43 (1H, t), 7.37 (1H, d), 7.35 (1H, d),
 4.85 (1H, sept), 4.52 (2H, br s), 3.63-3.54 (4H, br. m), 3.30 (2H, aparente dd),
 2.43 (2H, t), 2.06 (2H, quin), 1.36 (6H, d); m/z (ES) 447 $[\text{M}+\text{H}]^+$.

20

EJEMPLO 7**2-[(1-metiletil)oxi]-5-[3-(2-metil-1,2,3,4-tetrahidro-5-isoquinolinil)-1,2,4-oxadiazol-5-il]benzonitrilo**

5



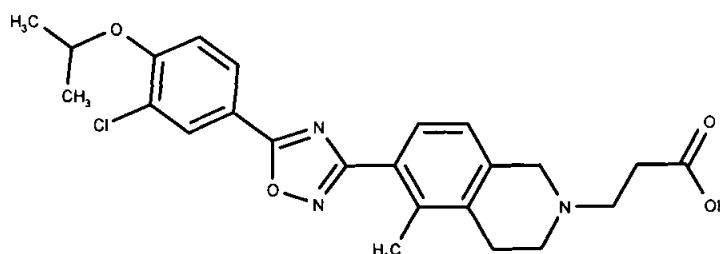
A una solución de 2-[(1-metiletil)oxi]-5-[3-(1,2,3,4-tetrahidro-5-isoquinolinil)-1,2,4-oxadiazol-5-il]benzonitrilo (Ejemplo 3, 25.0 mg, 0.069 mmoles) y formaldehído (37% p/v en H₂O, 8.0 μL, 0.10 mmoles) en DCM (5 mL) se añadió NaBH (OAc)₃ (29 mg, 0.14 mmoles) y la solución resultante fue agitada a temperatura ambiente durante 20 minutos. Se añadió salmuera (5 mL), y la capa acuosa fue extraída con DCM (5 mL). Las capas orgánicas combinadas fueron concentradas *in vacuo* para dar un sólido blanco. Este sólido fue redissuelto en DMSO-MeOH, agregado a un cartucho SCX y lavado con MeOH. El producto fue eluído con NH₃ en MeOH; la concentración *in vacuo* dio un sólido blanco (20.1 mg, 78%). RMN ¹H (400 MHz, CDCl₃) δ 8.41 (1H, d), 8.32 (1H, dd), 7.98 (1H, d), 7.29 (1H, t), 7.20 (1H, d), 7.12 (1H, d), 4.79 (1H, sept), 3.67 (2H, s), 3.30 (2H, t), 2.75 (2H, t), 2.49 (3H, s), 1.47 (6H, d).



EJEMPLO 8

Ácido 3-[6-(5-{3-Cloro-4-[(1-metiletil)oxil]fenil}-1,2,4-oxadiazol-3-il)-5-metil-3,4-dihidro-2(1H)-isoquinolinil]propanoico

5



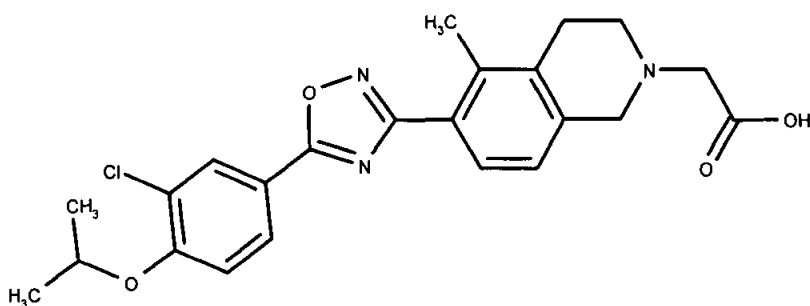
A una solución de etil 3-[6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-5-metil-3,4-dihidro-2(1H)-isoquinolinil] propanoato (Preparación 20; 90 mg; 0.186 mmoles) en etanol (2 ml) y THF (2 ml) a temperatura ambiente se añadió hidróxido de sodio 2N (0.186 ml; 0.372 mmoles), y la mezcla resultante fue agitada a temperatura ambiente durante aproximadamente 2.5 horas. La remoción de la mayor parte de los solventes, dilución con aproximadamente 1 ml de agua, seguido de adición de ácido acético (aproximadamente 300 μ l) dieron un precipitado. La mezcla fue extraída con diclorometano para dar, después de remoción del solvente y trituración con éter dietílico, el compuesto del título como un sólido blanco (40 mg).

RMN ^1H (DMSO- d_6) δ : 8.15 (d, 1H), 8.09 (dd, 1H), 7.64 (d, 1H), 7.43 (d, 1H), 7.09 (d, 1H), 4.88 (spt, 1H), 3.64 (s, 2H), 2.76 (br. s., 4H), 2.72 (t, 2H), 2.44 (t, 2H), 2.41 (s, 3H), 1.36 (d, 6H)

MS m/z 456 [MH^+]

EJEMPLO 9**Ácido [6-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-5-metil-3,4-dihidro-2(1H)-isoquinolinil]acético**

5



10

A una solución de etil [6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-5-metil-3,4-dihidro-2(1H)-isoquinolinil]acetato (Preparación 21; 75 mg; 0.16 mmoles) en etanol (2 ml) y THF (2 ml) a temperatura ambiente se añadió hidróxido de sodio 2N, y la mezcla resultante fue agitada a temperatura ambiente durante 40 minutos. Los solventes fueron retirados y el residuo fue disuelto en agua (aproximadamente 1 ml). Se añadió ácido acético (1 ml), todos los solventes fueron retirados y el residuo fue co-evaporado con tolueno para dar un sólido amarillo pálido. Este sólido fue triturado con éter dietílico para dar el compuesto del título, el cual fue filtrado como un sólido amarillo pálido (50 mg).

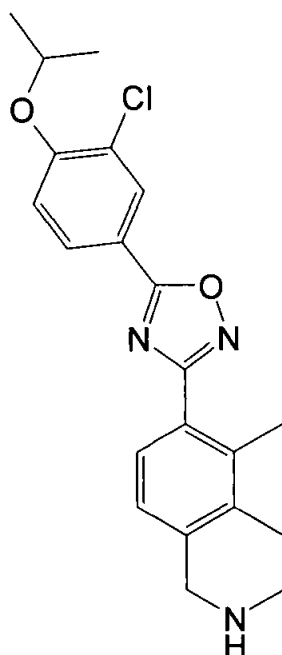
20

MS m/z 442 [MH⁺]

RMN ¹H (DMSO-d₆) δ: 8.16 (br. s., 1H), 8.10 (d, 1H), 7.62 (d, 1H), 7.44 (d, 1H), 7.05 (d, 1H), 4.88 (spt, 1H), 3.70 (br. s., 2H), 2.91 (br. s., 2H), 2.77 (br. s., 4H), 2.42 (br. s., 3H), 1.36 (d, 6H).

EJEMPLO 10

Trifluoroacetato de 6-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-5-metil-1,2,3,4-tetrahidroisoquinolina



10

15 A una solución de 1,1-dimetiletil 6-(5-{3-cloro-4-[(1-metiletil)oxi]
fenil}-1,2,4-oxadiazol-3-il)-5-metil- 3,4-dihidro-2(1H)- isoquinolincarboxilato
(Preparación 19; 210 mg; 0.434 mmoles) en diclorometano (3 ml) a 0°C se
agregó ácido trifluoroacético (3 ml) gota a gota. La mezcla resultante fue
agitada a 0°C durante 1 hora, dando una solución amarillo pálido. La remoción
20 del solvente y co-evaporación con tolueno dieron un sólido blanco, el cual fue
triturado con éter dietílico para dar el compuesto del título como un sólido
blanco (206 mg).

RMN ^1H (DMSO- d_6) δ : 9.08 (br. s., 2H), 8.17 (d, 1H), 8.10 (dd, 1H), 7.78 (d, 1H), 7.45 (d, 1H), 7.28 (d, 1H), 4.84 - 4.94 (m, 1H), 4.38 (br. s., 2H), 3.45 - 3.52 (m, 2H), 2.98 (t, 2H), 2.46 (s, 3H), 1.36 (d, 6H)

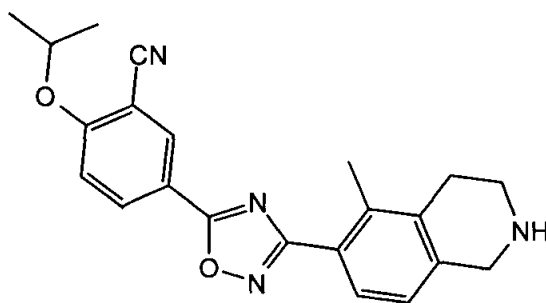
MS m/z 384 $[\text{MH}^+]$

5

EJEMPLO 11

Sal de ácido 2-[(1-Metiletil)oxi]-5-[3-(5-metil-1,2,3,4-tetrahidro-6-isoquinolinil)-1,2,4-oxadiazol-5-il]benzonitril trifluoroacético

10



15

Ácido trifluoroacético (3 ml) se añadió a una solución enfriada con hielo de 1,1-dimetiletil 6-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-5-metil-3,4-dihidro-2(1H)-isoquinolincarboxilato (Preparación 22; 486 mg, 1.02 mmoles) en diclorometano (3 ml). La mezcla de reacción fue agitada a 0°C durante 30 minutos. El solvente fue evaporado y el residuo co-evaporado de tolueno (x2). La trituración del residuo con éter dietílico dio el compuesto del título como un sólido incoloro el cual fue filtrado y secado (485 mg). RMN ^1H (400 MHz, CDCl_3) δ : 1.48 (6H, d), 2.54 (3H, s), 3.09 (2H, m), 3.5

20

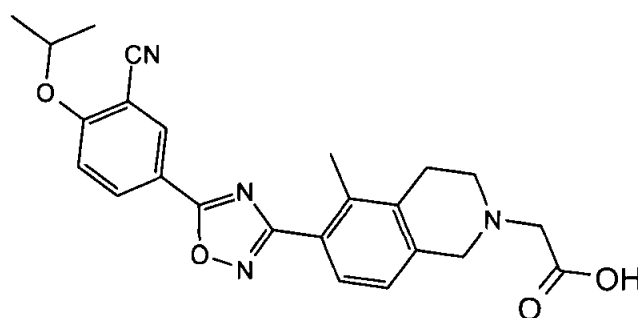
(2H, oscurecido por solvente residual), 4.36 (2H, s), 4.80 (1H, m), 7.08-7.15 (2H, m), 7.85 (1H, d), 8.33 (1H, d), 8.42 (1H, s), 10.20 (2H, br s). MS m/z 375 [MH]⁺.

5

EJEMPLO 12

Ácido [6-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-5-metil-3,4-dihidro-2(1H)-isoquinolinil]acético

10



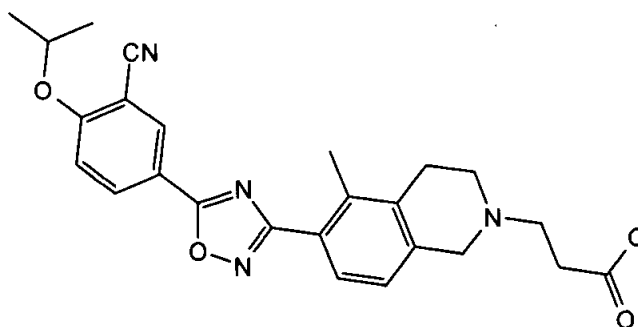
Hidróxido de sodio 2M (2 ml) se agregó a una suspensión de etil
 15 [6-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-5- metil-3,4-dihidro-
 2(1H)-isoquinolinil]acetato (Preparación 23; 80 mg, 0.17 mmoles) en etanol (2
 ml). La mezcla de reacción fue agitada a temperatura ambiente durante 2
 horas. El solvente fue evaporado y el residuo fue diluido con agua (5 ml). La
 solución fue acidificada con ácido acético y extraída con acetato de etilo (3x5
 20 ml). La fase acuosa fue evaporada y el residuo fue purificado mediante MDAP
 para dar el compuesto del título como un sólido incoloro (7 mg). RMN ¹H (400
 MHz, d₄MeOH) δ: 1.46 (6H, d), 2.55 (3H, s), 3.19 (2H, t), 3.35 (2H, s), 3.67
 (2H, t), 3.78 (2H, s), 4.53 (2H, s), 4.95 (1H, m) (parte oscurecida por pico de

agua), 7.20 (1H, d), 7.54 (1H, d), 7.85 (1H, d), 8.50-8.60 (2H, m). MS m/z 433 [MH]⁺.

EJEMPLO 13

5 Sal de sodio del ácido 3-[6-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-
oxadiazol-3-il)-5-metil-3,4-dihidro-2(1H)-isoquinolinil]propanoico

10



Hidróxido de sodio 2M (2 ml) se agregó a una solución de etil 3-[6-(5-{3-ciano-4- [(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)- 5-metil-3,4-dihidro-
15 2(1H)-isoquinolinil]propanoato (Preparación 24; 80 mg, 0.17 mmoles) en etanol (2 ml) a 60°C. La mezcla de reacción fue agitada a 60°C durante 2 horas, enfriada a temperatura ambiente y diluida con agua (2 ml). El sólido fue filtrado, lavado con una pequeña cantidad de agua y secado para dar el compuesto del título como un sólido incoloro (55 mg). RMN ¹H (400 MHz,
20 d₆DMSO) δ: 1.39 (6H, d), 2.08 (2H, t), 2.44 (3H, s), 2.59-2.78 (6H, m), 3.56 (2H, s), 4.98 (1H, m), 7.09 (1H, d), 7.55 (1H, d), 7.65 (1H, d), 8.40 (1H, dd), 8.50 (1H, s). MS m/z 447 [MH]⁺.

Preparación de membrana para ensayo GTP γ S de S1P1

Para preparaciones de membrana todos los pasos se realizaron a 4°C. Células de hepatoma de rata que expresan en forma estable el receptor S1P1 de humano o células de leucemia basofílica de rata (RBL) que expresan en forma estable el receptor S1P3 de humano fueron cultivadas a 80% de confluencia antes de ser recolectadas en 10 ml de solución salina de pH regulado con fosfato (PBS) y centrifugadas a 1200 rpm durante 5 minutos. Después de retirar el supernadante, la pella fue resuspendida y las células fueron homogenizadas dentro de un mezclador Waring de vidrio por 2 ráfagas de 15 segundos en 200 mls de regulador de pH (HEPES 50 mM, leupeptina 1 mM, 25 μ g/ml bacitracina, EDTA 1mM, PMSF 1mM, pepstatina A 2 μ M). El mezclador fue sumergido en hielo durante 5 minutos después de la primera ráfaga y 10-40 minutos después de la ráfaga final para dejar que la espuma se disipara. El material después se hizo girar a 500 g durante 20 minutos y el supernadante se hizo girar durante 36 minutos a 48,000 g. La pella fue resuspendida en el mismo regulador de pH que arriba pero sin PMSF y pepstatina A. Luego el material fue empujado a través de una aguja de 0.6 mm, fabricada al volumen requerido, (usualmente x4 el volumen de la pella de células original), se prepararon alícuotas con él y se almacenó congelado a -80°C.

Preparación de membrana alternativa para ensayo GTP γ S de

S1P1

Todos los pasos se realizaron a 4°C. Las células fueron homogenizadas dentro de un mezclador Waring de vidrio por 2 ráfagas de 15 segundos en 200 mls de regulador de pH (HEPES 50mM, leupeptina 1mM, 25µg/ml bacitracina, EDTA 1mM, PMSF 1mM, pepstatina A 2µM). El mezclador fue sumergido en hielo durante 5 minutos después de la primera ráfaga y 10-40 minutos después de la ráfaga final para dejar que la espuma se disipara. Luego el material se hizo girar a 500 g durante 20 minutos y el supernadante se hizo girar durante 36 minutos a 48,000 g. La pella fue resuspendida en el mismo regulador de pH que arriba pero sin PMSF y pepstatina A. Luego el material fue empujado a través de una aguja de 0.6 mm, hecha al volumen requerido, (usualmente x4 el volumen de la pella de células original), se prepararon alícuotas con él y se almacenó congelado a -80°C.

Ensayo GTP γ S de S1P1

Membranas de hepatoma de rata de S1P1 de humano (1.5 µg/cavidad) fueron adheridas a cuentas de ensayo de proximidad de centelleo (SPA) revestidas con aglutinina de germen de trigo (0.125 mg/cavidad) en regulador de pH de ensayo (HEPES 20mM, MgCl₂ 10mM, NaCl 100 mM y pH

ajustado a 7.4 usando KOH 5M, GDP 10 μ M FAC (concentración de ensayo final) y saponina 90 μ g/ml FAC se agregó también).

Después de 30 minutos de preacoplar en hielo la suspensión de cuentas y membranas fue colocada en una placa de cavidades LV384 (5 μ l/cavidad) de propileno Greiner blanca, que contenía 0.1 μ l del compuesto. 5 μ l/cavidad [^{35} S]-GTP γ S (0.5 nM concentración de radioligando final) hecho en regulador de pH de ensayo se añadió luego a placas de agonista. La mezcla de ensayo final (10.1 μ l) fue después centrifugada a 1000 rpm durante 5 minutos y leída inmediatamente en un lector Viewlux.

10 Todos los compuestos de prueba fueron disueltos en DMSO a una concentración de 10 mM y fueron preparados en 100% DMSO usando un paso de dilución de 1 en 4 para proveer curvas de respuesta a la dosis de 11 puntos. Las diluciones fueron transferidas a las placas de ensayo asegurando que la concentración de DMSO fuera constante en la placa para todos los
15 ensayos.

Todos los datos fueron normalizados a la media de 16 cavidades de control altas y 16 cavidades de control bajas en cada placa. Después se aplicó un ajuste de curva de cuatro parámetros.

20 Método alternativo para ensayo GTP γ S de S1P1

Membranas RH7777 que expresan S1P1 (1.5 μ g/cavidad) membranas (1.5 μ g/cavidad) fueron homogenizadas haciéndolas pasar a

través de una aguja 23G. Estas fueron después adheridas a cuentas de SPA revestidas con WGA (0.125 mg/cavidad) en regulador de pH de ensayo (HEPES 20 mM, $MgCl_2$ 10 mM, NaCl 100 mM y pH ajustado a 7.4 usando KOH 5M). GDP 10 μ M FAC y saponina 90 μ g/ml FAC se añadieron también.

- 5 Después de 30 minutos de preacoplar en hielo, la suspensión de cuentas y membranas fue colocada en placas de cavidades LV 384 (5 μ l/cavidad) de propileno Greiner blancas, que contenían 0.1 μ l del compuesto. 5 μ l/cavidad [^{35} S]-GTP γ S (0.5 nM para S1P1 o 0.3 nM para S1P3 concentración de radioligando final) hecho en regulador de pH de ensayo se
10 añadió luego a las placas. La mezcla de ensayo final (10.1 μ l) fue después sellada, se hizo girar en una centrífuga, después fue leída inmediatamente en un instrumento Viewlux.

- Los compuestos ejemplificados de la invención tuvieron un $pEC_{50} > 5$. Los ejemplos 1-7, 8, 9, 11-13 tuvieron un pEC_{50} de >7 . Los
15 ejemplos 2, 4, 6 y 8 tuvieron un pEC_{50} de >8 .

S1P3

- Membranas de S1P3 de células de leucemia basofílica de rata (RBL-2H3) (1.5 μ g/cavidad) fueron adheridas a cuentas de SPA revestidas de
20 WGA (0.125 mg/cavidad) en regulador de pH de ensayo (HEPES 20 mM, $MgCl_2$ 3 mM, NaCl 100 mM y pH ajustado a 7.4 usando KOH 5M), GDP 10 μ M FAC y saponina 90 μ g/ml FAC se añadieron también).

Después de 30 minutos de preacoplar en hielo, la suspensión de cuentas y membranas fue colocada en una placa de cavidades LV384 (5 μ l/cavidad) de propileno Greiner blanca, que contenía 0.1 μ l del compuesto. 5 μ l/cavidad [^{35} S]-GTP γ S (0.5 nM concentración de radioligando final) hecho en regulador de pH de ensayo se añadió luego a placas de agonista. La mezcla de ensayo final (10.1 μ l) fue centrifugada a 1000 rpm durante 5 minutos y luego leída inmediatamente en un lector Viewlux.

Todos los compuestos de prueba fueron disueltos en DMSO a una concentración de 10 mM y fueron preparados en 100% DMSO usando un paso de dilución de 1 en 4 para proveer curvas de respuesta a la dosis de 11 puntos. Las diluciones fueron transferidas a las placas de ensayo asegurando que la concentración de DMSO fuera constante en la placa para todos los ensayos.

Todos los datos fueron normalizados a la media de 16 cavidades de control altas y 16 cavidades de control bajas en cada placa. Después se aplicó un ajuste de curva de cuatro parámetros.

Método alternativo para ensayo GTP γ S de S1P3

Membranas RBL que expresan S1P3 (1.5 μ g/cavidad) fueron homogenizadas haciéndolas pasar a través de una aguja 23G. Estas fueron después adheridas a cuentas de SPA revestidas con WGA (0.125 mg/cavidad) en regulador de pH de ensayo (HEPES 20 mM, MgCl₂ 10 mM,

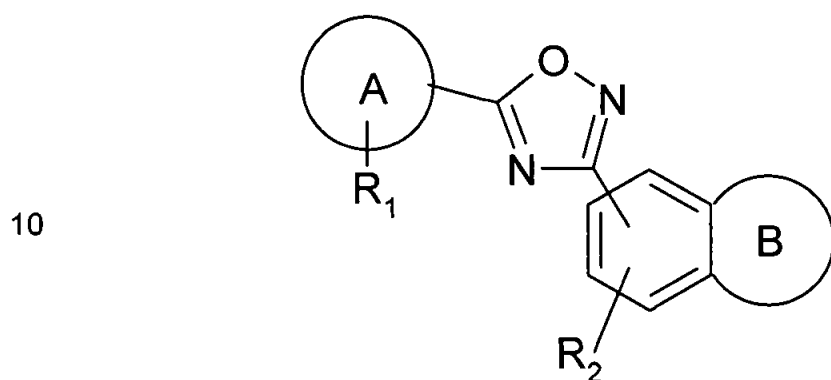
NaCl 100 mM y pH ajustado a 7.4 usando KOH 5M). GDP 10 μ M FAC y saponina 90 μ g/ml FAC se añadieron también.

Después de 30 minutos de preacoplar en hielo, la suspensión de cuentas y membranas fue colocada en placas de cavidades LV 384 (5 μ l/cavidad) de propileno Greiner blancas, que contenían 0.1 μ l del compuesto. 5 μ l/cavidad [^{35} S]-GTP γ S (0.5 nM para S1P1 o 0.3 nM para S1P3 concentración de radioligando final) hecho en regulador de pH de ensayo se añadió luego a las placas. La mezcla de ensayo final (10.1 μ l) fue después sellada, se hizo girar en una centrífuga, después fue leída inmediatamente en 10 un instrumento Viewlux.

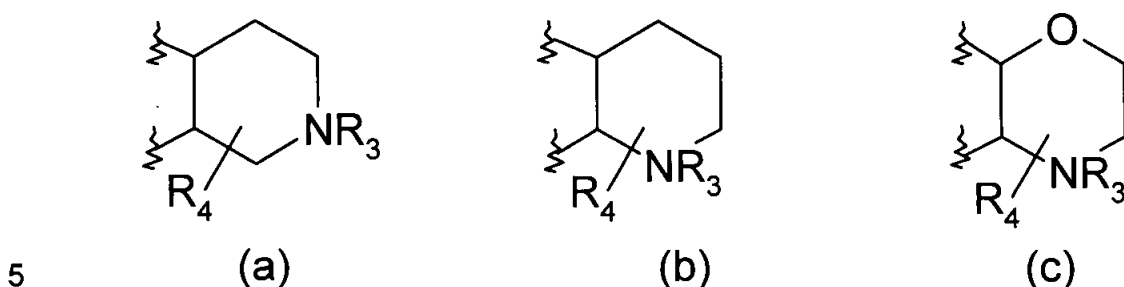
Los compuestos ejemplificados sometidos a prueba en este ensayo tuvieron un pEC50 < 6, muchos tuvieron un pEC50 <5. Los ejemplos 1, 4, 8-10, 12 y 13 tuvieron un pEC50 <5.

NOVEDAD DE LA INVENCION**REIVINDICACIONES**

- 5 1.- Un compuesto de fórmula (I) o una sal farmacéuticamente
aceptable del mismo:



- A es fenilo o un anillo de heteroarilo de 5 o 6 eslabones; R₁ es
15 hasta dos sustituyentes seleccionados independientemente de halógeno,
alcoxi C₍₁₋₃₎, fluoroalquilo C₍₁₋₃₎, ciano, fluoroalcoxi C₍₁₋₃₎, alquilo C₍₁₋₆₎ y
cicloalquilo C₍₃₋₆₎; R₂ es hidrógeno, halógeno o alquilo C₍₁₋₄₎; B se selecciona
de uno de los siguientes:



R_3 es hidrógeno, alquilo $C_{(1-3)}$ o $(CH_2)_{1-3}CO_2H$; R_4 es hidrógeno o alquilo $C_{(1-3)}$; cuando R_2 o R_4 es alquilo puede ser opcionalmente interrumpido por oxígeno.

10 2.- Un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, en donde: A es fenilo; R_1 es hasta dos sustituyentes independientemente seleccionados de cloro, isopropoxi y ciano; R_2 es hidrógeno o metilo; B es (a); R_3 es hidrógeno, metilo o $(CH_2)_{1-3}CO_2H$; R_4 es hidrógeno.

15 3.- Un compuesto seleccionado de: 5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,3,4-tetrahidroisoquinolina, 2-[(1-metiletil)oxi]-5-[3-(1,2,3,4-tetrahidro-5-isoquinolinil)-1,2,4-oxadiazol-5-il] benzonitrilo, ácido [5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-3,4-dihidro-2(1H)-isoquinolinil]acético, ácido 3-[5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-3,4-dihidro-2(1H)-isoquinolinil]propanoico, ácido 4-[5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-3,4-dihidro-2(1H)-isoquinolinil]butanoico, 2-[(1-metiletil)oxi]-5-[3-(2-metil-1,2,3,4-tetrahidro-5-isoquinolinil)-1,2,4-oxadiazol-5-il]benzonitrilo, ácido [8-(5-{3-Cloro-4-[(1-

20

metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-3,4- dihidro-2H-cromen-4-il] acético, ácido 3-[6-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-5-metil-3,4-dihidro-2(1H)-isoquinolinil]propanoico, ácido [6-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-5-metil-3,4-dihidro-2(1H)-isoquinolinil]acético, 6-(5-
5 {3-Cloro-4-[(1-metiletil)oxi] fenil}-1,2,4-oxadiazol-3-il)-5- metil-1,2,3,4-tetrahidroisoquinolina, 2-[(1-Metiletil)oxi]-5-[3-(5-metil-1,2,3,4-tetrahidro-6-isoquinolinil)-1,2,4-oxadiazol-5-il]benzonitrilo, ácido [6-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-5-metil-3,4-dihidro-2(1H)-isoquinolinil]acético, ácido 3-[6-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-5-
10 metil-3,4-dihidro-2(1H)-isoquinolinil]propanoico, y sales farmacéuticamente aceptable de los mismos.

4.- El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 3 para el tratamiento de condiciones o trastornos mediados por los receptores S1P1.

15 5.- El uso de conformidad con la reivindicación 4, en donde la condición o trastorno es esclerosis múltiple, enfermedades autoinmunes, trastornos inflamatorios crónicos, asma, neuropatías inflamatorias, artritis, trasplante, enfermedad de Crohn, colitis ulcerativa, lupus eritematoso, psoriasis, lesión por reperfusión por isquemia, tumores sólidos y metástasis
20 tumoral, enfermedades asociadas con angiogénesis, enfermedades vasculares, condiciones de dolor, enfermedades virales agudas, condiciones inflamatorias de intestino, diabetes dependiente de insulina y no dependiente de insulina.

6.- El uso de conformidad con la reivindicación 4, en donde la condición es lupus eritematoso.

7.- El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 3 para fabricar un medicamento para usar en el
5 tratamiento de condiciones o trastornos mediados por los receptores S1P1.

8.- El uso de conformidad con la reivindicación 7, en donde la condición o trastorno es esclerosis múltiple, enfermedades autoinmunes, trastornos inflamatorios crónicos, asma, neuropatías inflamatorias, artritis, trasplante, enfermedad de Crohn, colitis ulcerativa, lupus eritematoso,
10 psoriasis, lesión por reperfusión por isquemia, tumores sólidos y metástasis tumoral, enfermedades asociadas con angiogénesis, enfermedades vasculares, condiciones de dolor, enfermedades virales agudas, condiciones inflamatorias del intestino, diabetes dependiente de insulina y no dependiente de insulina.

15 9.- El uso de conformidad con la reivindicación 7, en donde la condición es lupus eritematoso.

10.- Una composición farmacéutica que comprende un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 3.

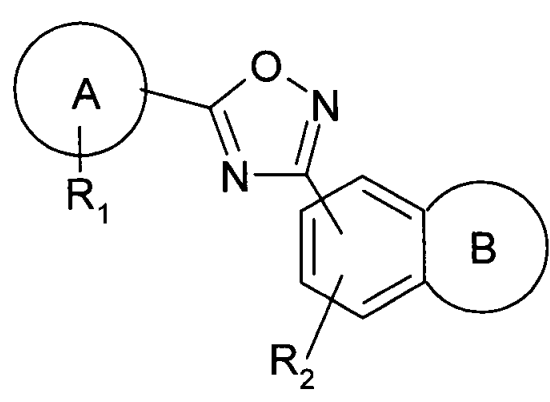
11.- Un método de tratamiento para condiciones o trastornos
20 en mamíferos incluyendo humanos que pueden ser mediados vía los receptores S1P1, que comprende administrar al sujeto que padece la condición o trastorno una cantidad terapéuticamente segura y efectiva de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo.

RESUMEN DE LA INVENCIÓN

La presente solicitud describe compuestos a base de oxadiazol
de fórmula (I)

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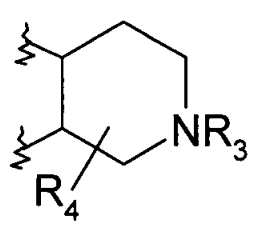


(I)

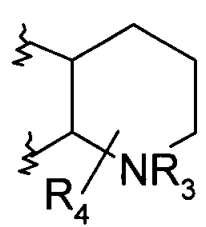
activos en 1-fosfato de esfingosina (S1P) en particular útiles para
tratar lupus eritematoso; A es fenilo o un anillo de heteroarilo de 5 o 6
eslabones; B se selecciona de uno de los siguientes: fórmulas: (a) (b) (c).

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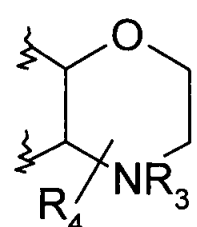
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(a)



(b)



(c)

37B

P10/705F

PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

GlaxoSmithKline Services Unlimited
980 Great West Road
Brentford
Middlesex TW8 9GS
GRANDE BRETAGNE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing
(day/month/year)

17.03.2010

Applicant's or agent's file reference
JEG/PB62782

IMPORTANT NOTIFICATION

International application No.
PCT/EP2008/067963

International filing date (day/month/year)
19.12.2008

Priority date (day/month/year)
21.12.2007

Applicant
GLAXO GROUP LIMITED et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/B/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international
preliminary examining authority:



European Patent Office P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040
Fax: +31 70 340 - 3016

Authorized Officer

Cardenas, Claudette

Tel. +31 70 340-3370



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JEG/PB62782	FOR FURTHER ACTION		See Form PCT/PEA/416
International application No. PCT/EP2008/067963	International filing date (day/month/year) 19.12.2008	Priority date (day/month/year) 21.12.2007	
International Patent Classification (IPC) or national classification and IPC INV. C07D413D4			
Applicant GLAXO GROUP LIMITED et al			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>6</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ sent to the applicant and to the International Bureau) a total of <u>3</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions). ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).			
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ Box No. II Priority ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement ☐ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application ☒ Box No. VIII Certain observations on the international application			
Date of submission of the demand 2009-05-29		Date of completion of this report 17.03.2010	
Name and mailing address of the international preliminary examining authority:  European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016		Authorized officer Skulj, Primoz Telephone No. +31 70 340-1960	



INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2008/067963

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))
2. With regard to the **elements*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

Description, Pages

1-46 as originally filed

Claims, Numbers

1-11 as amended (together with any statement) under Art. 19 PCT

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
 4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
 5. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 70.2 (e)).
 6. ☐ Supplementary international search report(s) from Authority(ies) have been received and taken into account in drawing up this report (Rule 45bis.8(b) and (c)).

INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY

International application No.
PCT/EP2008/067963

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-11</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-11</u>
Industrial applicability (IA)	Yes: Claims	<u>1-11</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents (the numbering is continued from the Chapter I procedure):

- D3 WO 2007/116866 A (ASTELLAS PHARMA INC [JP]; HARADA HIRONORI [JP]; HATTORI KAZUYUKI [JP];) 18 October 2007 (2007-10-18) cited in the application ; & EP 2 003 132 A (ASTELLAS PHARMA INC [JP]) 17 December 2008 (2008-12-17)
- D4 NIGEL COOKEA ET AL: "Sphingosine 1-Phosphate Type 1 Receptor Modulators: Recent Advances and Therapeutic Potential" ANNUAL REPORTS IN MEDICINAL CHEMISTRY, SAN DIEGO, US, vol. 42, 1 January 2007 (2007-01-01) , pages 245-263, XP008102308 ISSN: 0065-7743 [retrieved on 2007-11-07]
- D5 VACHAL PETR ET AL: "Highly selective and potent agonists of sphingosine-1-phosphate 1 (S1P1) receptor." BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 15 JUL 2006, vol. 16, no. 14, 15 July 2006 (2006-07-15) , pages 3684-3687, XP002515397 ISSN: 0960-894X
- D6 YAN LIN ET AL: "SAR studies of 3-arylpropionic acids as potent and selective agonists of sphingosine-1-phosphate receptor-1 (S1P1) with enhanced pharmacokinetic properties." BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 1 FEB 2007, vol. 17, no. 3, 1 February 2007 (2007-02-01) , pages 828-831, XP002515921 ISSN: 0960-894X

1. Amendments

The amendments do not extend beyond the application as originally filed.

2. Note

Claims 10,11 relate to subject matter considered by this Authority to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT. The patentability can be dependant upon the wording of these claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

3. Novelty

The present application is novel in the sense of Article 33(2) PCT.

4. Inventive step

The present application does not meet the criteria of Article 33(3) PCT, because the subject-matter of claims 1-11 does not involve an inventive step for the following reasons:

D4 provides an overview of the compounds active on S1P. It cites documents D5 and D6, which also reference each other.

The structure of S1P active compounds is known from D5 to be composed of a left-hand side aromatic substituent, connected via a central heterocycle to a phenyl [see Figure 1]. D5 proposes the presently preferred cyano, isopropyl and chloro substituents on the left-hand side aromatic substituent which is phenyl or pyridyl [see Tables 1,3].

D6 [see Fig 1] discloses the same lead compound as D5 and indicates positions for modifications.

The instant compounds **differ** from said lead compound **only in that an additional 6-membered saturated heteroring has been condensed to the phenyl ring** on the right side of the compound.

D3 discloses S1P active compounds which share a structure of a bicyclic aromatic substituent (made of a 6 - membered ring **condensed** to either a 5 - or a 6 - membered ring), connected via the oxadiazole to phenyl or pyridyl. [see claim 1].

The instant **differ** from compounds of D3 when B (as defined in present claim 1) is either structure (a) or structure (c) **by an another bicyclic ring system** and where B has the structure (b) they represents **further selections** from D3. [the selection of structure (b) from 12 possibilities for R4 of D3, the selection (or modification) from a list of substituents for R1].

The objective technical problem is seen as the provision of alternative S1P active compounds useful to treat lupus erythematosus. The solution is provided with the instant compounds, their compositions and uses.

A skilled person would follow the suggestion for modification of a lead compound from D6, he would further know the advantage of modification by blocking the benzylic position (cyclizing onto the phenyl ring) [see D4, p.257]. He would be aware of D3 and would have tried alternative to bicyclic compound 23 of D4 by another cyclization (using one of the possibilities of claim 1 of D3) onto the phenyl ring, thus arriving at the present compounds.

Therefore the problem underlying the present application can no longer be seen in simply the provision of compounds active on S1P . The objective technical problem to be solved could now only be seen in the provision of additional structurally similar compounds for the same use **possessing any unexpected properties** over those already known.

In the absence of the comparative data substantiating **any unexpected properties of the instant compounds**, these compounds, their pharmaceutical compositions and applications do not involve an inventive step.

5. Industrial application

The claimed compounds are useful in medicine, consequently they fulfill the criteria of Article 33(4) PCT.

Re Item VIII

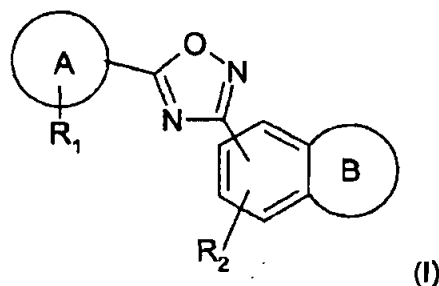
The independant claim 2 contains all the features of the independant claim 1, and should be made dependant (Rule 6.4 PCT).

Scope of protection is rendered unclear by the incorporations by reference, such as on p. 18.

It is assumed that the terms fluoroalkyl and fluoroalkoxy allow multiple fluoro substitutions, CF₃ was considered comprised within term fluoroalkyl.

Claims

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



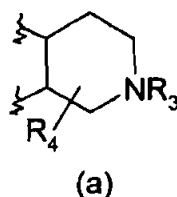
wherein

A is phenyl;

R₁ is up to two substituents independently selected from chloro, isopropoxy, and cyano;

R₂ is hydrogen or methyl ;

B is:



R₃ is hydrogen, methyl or (CH₂)₁₋₃CO₂H;

R₄ is hydrogen.

2. A compound selected from:

5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,3,4-tetrahydroisoquinoline

2-[(1-methylethyl)oxy]-5-[3-(1,2,3,4-tetrahydro-5-isoquinoliny)-1,2,4-oxadiazol-5-yl]benzonitrile

[5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1*H*)-isoquinoliny]acetic acid

3-[5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1*H*)-isoquinoliny]propanoic acid

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4-[5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2(1H)-isoquinoliny]butanoic acid

2-[(1-methylethyl)oxy]-5-[3-(2-methyl-1,2,3,4-tetrahydro-5-isoquinoliny)-1,2,4-oxadiazol-5-yl]benzonitrile

[8-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-3,4-dihydro-2H-chromen-4-yl]acetic acid

3-[6-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinoliny]propanoic acid

[6-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinoliny]acetic acid

6-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-1,2,3,4-tetrahydroisoquinoline

2-[(1-Methylethyl)oxy]-5-[3-(5-methyl-1,2,3,4-tetrahydro-6-isoquinoliny)-1,2,4-oxadiazol-5-yl]benzonitrile

[6-(5-{3-Cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinoliny]acetic acid

3-[6-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-5-methyl-3,4-dihydro-2(1H)-isoquinoliny]propanoic acid

and pharmaceutically acceptable salts thereof.

3. Use of a compound according to any one of claims 1 to 2 for the treatment of conditions or disorders mediated by S1P1 receptors.

4. Use according to claim 3, wherein the condition or disorder is multiple sclerosis, autoimmune diseases, chronic inflammatory disorders, asthma, inflammatory neuropathies, arthritis, transplantation, Crohn's disease, ulcerative colitis, lupus erythematosus, psoriasis, ischemia-reperfusion injury, solid tumours, and tumour metastasis, diseases associated with angiogenesis, vascular diseases, pain

153.

conditions, acute viral diseases, inflammatory bowel conditions, insulin and non-insulin dependant diabetes.

5. Use according to claim 3, wherein the condition is lupus erythematosus.

6. Use of a compound according to any one of claims 1 to 2 to manufacture a medicament for use in the treatment of conditions or disorders mediated by S1P1 receptors.

7. Use according to claim 6, wherein the condition or disorder multiple sclerosis, autoimmune diseases, chronic inflammatory disorders, asthma, inflammatory neuropathies, arthritis, transplantation, Crohn's disease, ulcerative colitis, lupus erythematosus, psoriasis, ischemia-reperfusion injury, solid tumours, and tumour metastasis, diseases associated with angiogenesis, vascular diseases, pain conditions, acute viral diseases, inflammatory bowel conditions, insulin and non-insulin dependant diabetes.

8. Use according to claim 6, wherein the condition is lupus erythematosus.

9. A pharmaceutical composition comprising a compound according to any one of claims 1 to 2.

10. A method of treatment for conditions or disorders in mammals including humans which can be mediated via the S1P1 receptors which comprises administering to the sufferer a therapeutically safe and effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

11. A method of treatment according to claim 10, wherein the condition is lupus erythematosus.

AMENDED SHEET

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

GLAXOSMITHKLINE
Attn. Griffith, Johanna Elise
Corporate Intellectual Property (CN925.1)
980 Great West Road
Brentford, Middlesex TW8 9GS
GRANDE BRETAGNE

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year)

06/03/2009

Applicant's or agent's file reference

JEG/PB62782

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/EP2008/067963

International filing date
(day/month/year)

19/12/2008

Applicant

GLAXO GROUP LIMITED

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority



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

Authorized officer

Petronella Elsackers

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference JEG/PB62782	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, Item 5 below.	
International application No. PCT/EP2008/067963	International filing date (day/month/year) 19/12/2008	(Earliest) Priority Date (day/month/year) 21/12/2007
Applicant GLAXO GROUP LIMITED		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6b/s(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

- ☐ the text is approved as submitted by the applicant
☒ the text has been established by this Authority to read as follows:

OXADIAZOLE DERIVATIVES ACTIVE ON SPHINGOSINE-1-PHOSPHATE (S1P)

5. With regard to the **abstract**,

- ☐ the text is approved as submitted by the applicant
☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
- b. ☐ none of the figures is to be published with the abstract

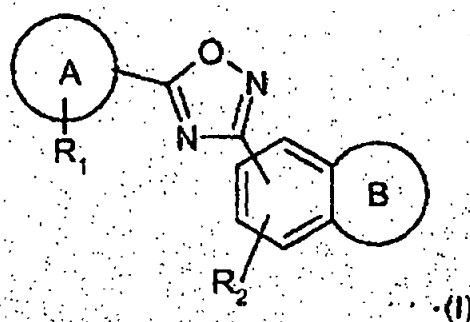
INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP2008/067963

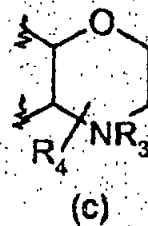
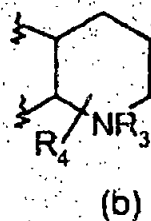
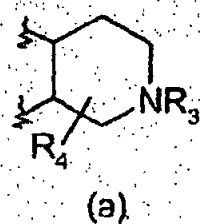
Box No. IV Text of the abstract (Continuation of Item 5 of the first sheet)

The present application discloses oxadiazole based compounds of formula (I) active on sphingosine-1-phosphate (S1P) in particular useful to treat lupus erythematosus.



A is phenyl or a 5 or 6-membered heteroaryl ring;

B is selected from one of the following:



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/067963

15A

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D413/04 C07D217/06 C07D217/22 C07D217/16 A61P37/00
A61P17/00 A61K31/4725 C07D413/14

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 A61P

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

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

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 760 071 A (ONO PHARMACEUTICAL CO [JP]) 7 March 2007 (2007-03-07) claims 1-32; example 62	1
X	EP 1 826 197 A (ONO PHARMACEUTICAL CO [JP]) 29 August 2007 (2007-08-29) claims 1-31; examples 13-4	1
X	WO 2007/116866 A (ASTELLAS PHARMA INC [JP]; HARADA HIRONORI [JP]; HATTORI KAZUYUKI [JP];) 18 October 2007 (2007-10-18) cited in the application example 40 & EP 2 003 132 A (ASTELLAS PHARMA INC [JP]) 17 December 2008 (2008-12-17)	1
Y	claim 1 ----- -/--	1-12

☒ 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.

G document member of the same patent family

Date of the actual completion of the international search

24 February 2009

Date of mailing of the international search report

06/03/2009

Name and mailing address of the ISA/

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

Authorized officer

Skulj, Primoz

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/067963

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NIGEL COOKE ET AL: "Sphingosine 1-Phosphate Type 1 Receptor Modulators: Recent Advances and Therapeutic Potential" ANNUAL REPORTS IN MEDICINAL CHEMISTRY, SAN DIEGO, US, vol. 42, 1 January 2007 (2007-01-01), pages 245-263, XP008102308 ISSN: 0065-7743 [retrieved on 2007-11-07] page 254 - page 257; compounds 20,21,23,24 -----	1-12
Y	VACHAL PETR ET AL: "Highly selective and potent agonists of sphingosine-1-phosphate 1 (S1P1) receptor." BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 15 JUL 2006, vol. 16, no. 14, 15 July 2006 (2006-07-15), pages 3684-3687, XP002515397 ISSN: 0960-894X figure 1; tables 1-3 -----	1-12
Y	YAN LIN ET AL: "SAR studies of 3-arylpropionic acids as potent and selective agonists of sphingosine-1-phosphate receptor-1 (S1P1) with enhanced pharmacokinetic properties." BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 1 FEB 2007, vol. 17, no. 3, 1 February 2007 (2007-02-01), pages 828-831, XP002515921 ISSN: 0960-894X figure 1 -----	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/067963

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Patent document cited in search report		Publication date		Patent family member(s)		Publication date
EP 1760071	A	07-03-2007	WO	2006001463 A1		05-01-2006
			US	2008207584 A1		28-08-2008
EP 1826197	A	29-08-2007	AU	2005314938 A1		22-06-2006
			CA	2591399 A1		22-06-2006
			WO	2006064757 A1		22-06-2006
			KR	20070091013 A		06-09-2007
WO 2007116866	A	18-10-2007	AU	2007236707 A1		18-10-2007
			CA	2648303 A1		18-10-2007
			EP	2003132 A1		17-12-2008
EP 2003132	A	17-12-2008	AU	2007236707 A1		18-10-2007
			CA	2648303 A1		18-10-2007
			WO	2007116866 A1		18-10-2007

PATENT COOPERATION TREATY

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From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2008/067963

International filing date (day/month/year)
19.12.2008

Priority date (day/month/year)
21.12.2007

International Patent Classification (IPC) or both national classification and IPC
INV. C07D413/04 C07D217/06 C07D217/22 C07D217/16 A61P37/00 A61P17/00 A61K31/4725 C07D413/14

Applicant
GLAXO GROUP LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patentlaag 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx. 31 651 epo nl
Fax: +31 70 340 - 3016

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Skulj, Primoz

Telephone No. +31 70 340-1960



Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>2,3</u>
	No: Claims	<u>1,4-12</u>
Inventive step (IS)	Yes: Claims	/
	No: Claims	<u>1-12</u>
Industrial applicability (IA)	Yes: Claims	<u>1-12</u>
	No: Claims	/

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V.

Reference is made to the following documents:

- D1: EP-A-1 760 071
- D2: EP-A-1 826 197
- D3: WO 2007/116866 A cited in the application
- D4: NIGEL COOKEA ET AL: "Sphingosine 1-Phosphate Type 1 Receptor Modulators: Recent Advances and Therapeutic Potential" ANNUAL REPORTS IN MEDICINAL CHEMISTRY, SAN DIEGO, US, vol. 42, pages 245-263, XP008102308 ISSN: 0065-7743 [retrieved on 2007-11-07]
- D5: VACHAL PETR ET AL: "Highly selective and potent agonists of sphingosine-1-phosphate 1 (S1P1) receptor." BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 15 JUL 2006, vol. 16, no. 14, 15 July 2006, pages 3684-3687, XP002515397 ISSN: 0960-894X
- D6: YAN LIN ET AL: "SAR studies of 3-arylpropionic acids as potent and selective agonists of sphingosine-1-phosphate receptor-1 (S1P1) with enhanced pharmacokinetic properties." BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 1 FEB 2007, vol. 17, no. 3, 1 February 2007, pages 828-831, XP002515921 ISSN: 0960-894X

The present application relates to the compounds active on sphingosine-1-phosphate (S1P).

1 Note

Claims 11,12 relate to subject matter considered by this Authority to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT. The patentability can be dependant upon the wording of these claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

2 Novelty (A.33(2) PCT)

The claimed subject matter of the claim 1 is not new in the sense of Article 33(2) PCT.

D1 to D3 all disclose compounds falling under the scope of present claim 1 active on S1P. Example 62 and the claims of D1, Example 13-4 and the claims of D2 anticipate the independent claim 1, and the use and composition claims in as much as they refer to known compounds. The same applies for the Example 40 of D3, which discloses a CF₃ substituent, which is considered to fall under the term fluoroalkyl.

The compounds defined in claims 2 and 3, their uses and composition are novel.

3 Inventive Step (33(3) PCT)

No inventive step can be recognized for the subject-matter which is not novel.

D4 provides an overview of the compounds active on S1P. It cites documents D5 and D6, which also reference each other.

The structure of S1P active compounds is known from D5 to be composed of a left-hand side aromatic substituent, connected via a central heterocycle to a phenyl [see Figure 1]. D5 proposes the presently preferred cyano, isopropyl and chloro substituents on the left-hand side aromatic substituent which is phenyl or pyridyl [see Tables 1,3].

D6 [see Fig 1] discloses the same lead compound as D5 and indicates positions for modifications.

The instant compounds **differ** from said lead compound **only in that an additional 6-membered saturated heteroring has been condensed to the phenyl ring** on the right side of the compound.

D3 discloses S1P active compounds which share a structure of a bicyclic aromatic substituent (made of a 6-membered ring **condensed** to either a 5- or a 6-membered ring), connected via the oxadiazole to phenyl or pyridyl. [see claim 1].

The instant **differ** from compounds of D3 when B (as defined in present claim 1) is either structure (a) or structure (c) **by an another bicyclic ring system** and where B has the structure (b) they represents **further selections** from D3. [the selection of structure (b) from 12 possibilities for R₄ of D3, the selection (or modification) from a list of substituents for R₁].

The objective technical problem is seen as the provision of alternative S1P active compounds useful to treat lupus erythematosus. The solution is provided with the instant compounds, their compositions and uses.

A skilled person would follow the suggestion for modification of a lead compound from D6, he would further know the advantage of modification by blocking the benzylic position (cyclizing onto the phenyl ring) [see D4, p.257]. He would be aware of D3 and would have tried alternative to bicyclic compound 23 of D4 by another cyclization (using one of the possibilities of claim 1 of D3) onto the phenyl ring, thus arriving at the present compounds.

Therefore the problem underlying the present application can no longer be seen in simply the provision of compounds active on S1P. The objective technical problem to be solved could now only be seen in the provision of additional structurally similar compounds for the same use **possessing any unexpected properties** over those already known.

In the absence of the comparative data substantiating **any unexpected properties of the instant compounds**, these compounds, their pharmaceutical compositions and applications do not comply with the requirements of the Article 33(3) PCT.

It is further noted, that all the exemplified compounds possess the structure having R1 = isopropoxy, chloro, or cyano as defined in claim 2, and only for those compounds the assays described in the present application confirm the pharmacological effect.

The scope of claim 1 covers also other novel structures not covered by the claim 2, which are however supported by no example. For such compounds the problem cannot be considered as solved over the entire scope of claims 1.

3 Industrial Application (A.33(4) PCT)

The claimed compounds are useful in medicine, consequently they fulfill the criteria of Article 33(4) PCT.

Re Item VIII.

The independant claims 2,3 contain all the features of the independant claim 1, and should be made dependant (Rule 6.4 PCT).

Scope of protection is rendered unclear by the incorporations by reference, such as on p. 18.

It is assumed that the terms fluoroalkyl and fluoroalkoxy allow multiple fluoro substitutions, CF₃ was considered comprised within term fluoroalkyl.

In case the applicant does not limit the invention to the exemplified group of compounds as defined in claim 2, a unity of invention objection may arise.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/067963

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D413/04 C07D217/06 C07D217/22 C07D217/16 A61P37/00
A61P17/00 A61K31/4725 C07D413/14

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 A61P

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

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

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 760 071 A (ONO PHARMACEUTICAL CO [JP]) 7 March 2007 (2007-03-07) claims 1-32; example 62 -----	1
X	EP 1 826 197 A (ONO PHARMACEUTICAL CO [JP]) 29 August 2007 (2007-08-29) claims 1-31; examples 13-4 -----	1
X	WO 2007/116866 A (ASTELLAS PHARMA INC [JP]; HARADA HIRONORI [JP]; HATTORI KAZUYUKI [JP];) 18 October 2007 (2007-10-18) cited in the application example 40 & EP 2 003 132 A (ASTELLAS PHARMA INC [JP]) 17 December 2008 (2008-12-17) claim 1 -----	1
Y	----- -/--	1-12

☒ 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

24 February 2009

Date of mailing of the international search report

06/03/2009

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Skulj, Primož

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/067963

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NIGEL COOKE ET AL: "Sphingosine 1-Phosphate Type 1 Receptor Modulators: Recent Advances and Therapeutic Potential" ANNUAL REPORTS IN MEDICINAL CHEMISTRY, SAN DIEGO, US, vol. 42, 1 January 2007 (2007-01-01), pages 245-263, XP008102308 ISSN: 0065-7743 [retrieved on 2007-11-07] page 254 - page 257; compounds 20,21,23,24 -----	1-12
Y	VACHAL PETR ET AL: "Highly selective and potent agonists of sphingosine-1-phosphate 1 (S1P1) receptor." BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 15 JUL 2006, vol. 16, no. 14, 15 July 2006 (2006-07-15), pages 3684-3687, XP002515397 ISSN: 0960-894X figure 1; tables 1-3 -----	1-12
Y	YAN LIN ET AL: "SAR studies of 3-arylpropionic acids as potent and selective agonists of sphingosine-1-phosphate receptor-1 (S1P1) with enhanced pharmacokinetic properties." BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 1 FEB 2007, vol. 17, no. 3, 1 February 2007 (2007-02-01), pages 828-831, XP002515921 ISSN: 0960-894X figure 1 -----	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/067963

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
EP 1760071	A	07-03-2007	WO	2006001463 A1	05-01-2006
			US	2008207584 A1	28-08-2008
EP 1826197	A	29-08-2007	AU	2005314938 A1	22-06-2006
			CA	2591399 A1	22-06-2006
			WO	2006064757 A1	22-06-2006
			KR	20070091013 A	06-09-2007
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			CA	2648303 A1	18-10-2007
			EP	2003132 A1	17-12-2008
EP 2003132	A	17-12-2008	AU	2007236707 A1	18-10-2007
			CA	2648303 A1	18-10-2007
			WO	2007116866 A1	18-10-2007



No. 10-074471- .00000-0000

Fecha: 2010-06-21 17:06:21 Dep: 2020 DIR NUEVASCR
Tra: 11 PATENTEIYII Eve: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 169

PATENTE DE INVENCION ☐

MODELO DE UT.

- ☐ Indicación que se solicita 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 (De ser el caso formato de descuento)
- Completa ☐ Incompleta ☐

PATENTE DE INVENCION PCT ☒ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

- ☒ Indicación que se solicita una PCT
 - ☒ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
 - ☐ Dibujos de ser estos pertinentes
 - ☒ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)
- Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐

(Art. 119 Decisión 486/00)

- ☐ Indicación que se solicita 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 ☐

(Art. 92 Decisión 486/00)

- ☐ Indicación que se solicita un esquema de trazado
 - ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
 - ☐ Representación gráfica de un esquema de trazado
 - ☐ Comprobante de pago de las tasas establecidas
- Completa ☐ Incompleta ☐



Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
GLAXO GROUP LIMITED

REFERENCIA	Radicación No.	10 074471
	Solicitud internacional	PCT/EP2008/067963
	Fecha inicio fase nacional	21/07/2010
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	10540

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. Si fuere el caso, el solicitante debe adjuntar la traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT.
2. 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.

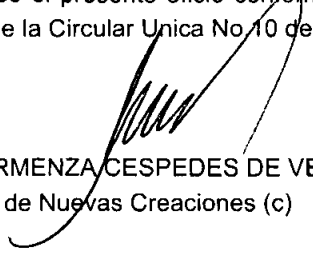
Continúa en la página siguiente...



Continuación radicado No: 10 074471



Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 20 AGO. 2010
adpa11



Bogotá D.C.,
2020



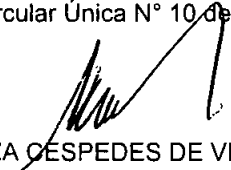
Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
GLAXO GROUP LIMITED

REFERENCIA	Radicación No.	10 074471
	Solicitud internacional	PCT/EP2008/067963
	Fecha inicio fase nacional	21/07/2010
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	10541

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de diez reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

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 N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

20 AGO. 2010

El anterior requerimiento fue notificado por fijación en lista de fecha _____.
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