CSA836221
Organización y Digitalización CSA Ltda

PCT

Industria y Comercio

SUPERINTENDENCIA

10-74455 ½

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

SOLICITUD DE PATENTE DE INVENCIÓN

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

SOLICITANTE: GLAXO GROUP LIMITED.

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

APODERADO: CARLOS R. OLARTE

BOGOTÁ Junio de 2009

P2010/000084

21-07-2010
No Exam

OLARTERAISBECK

OLARTE RAISBECK MOURE

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-074455- -00000-0000
Fecha: 2010-06-21 16:58:04 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 359

PETITORIO - FORMULARI
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2010/000084**

SOLICITUD DE:

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] 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.** [X] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** _____ **Número** 79782747Bta **TP** 74.295
INVENTOR (ES) (72)	**Nombre:** VER PAGINA ADJUNTA **Dirección:** VER PAGINA ADJUNTA **Nacionalidad O Domicilio:** VER PAGINA ADJUNTA	

(5) **PCT (86)**

Solicitud Internacional No. PCT/EP2008/067965 Fecha Diciembre 19, 2008

Publicación Internacional No. WO 2009/080725 Fecha Julio 02, 2009

(6) **Título (54)** **DERIVADOS DE OXADIAZOL ACTIVOS SOBRE FOSFATO DE ESFINGOSINA-1**

Clasificación Internacional (51) C07D 413/04, C07D413/14, C07D 223/16, C07D 267/14, C07D 271/06, A61P 37/00, A61P 17/00, A61K 31/55

Prioridad **SI** [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
GB	Diciembre 21, 2007	0725120.0
GB	Diciembre 01, 2008	0821918.0

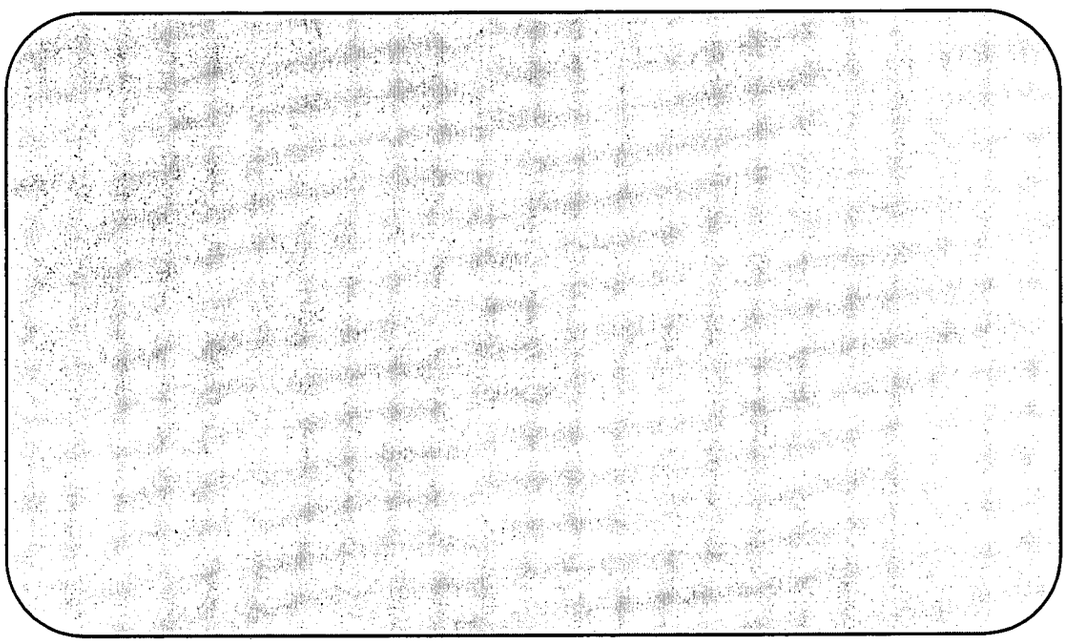
(9) **Comprobante de pago No.** 10- **Fecha** Junio De 2010

(10) **ANEXOS**

2

[x]	Comprobante de pago de la tasa de presentación de la solicitud.
[x]	Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
[x]	Poderes, si fuere el caso. Adjunto copia simple ver Expediente No. 06-018.321
[ ]	Documento de cesión del inventor al solicitante o a su causante.
[ ]	Declaraciones.
[x]	Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
[x]	Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
[ ]	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.
[x]	Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**



( ) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

C.C. 79.782.747 Bta T.P. 74.295

LISTA DE INVENTORES

PCT/EP2008/067965

Emmanuel Hubert DEMONT,
GlaxoSmithkline, Gunnels
Wood Road, Stevenage Hertfordshire
SG1 2NY
Gran Bretaña
Nacionalidad: Francesa

Jag Paul HEER,
GlaxoSmithkline, New Forntiers
Science Park South,
Third Avenue, Harlow Essex CM19 5AW
Gran Bretaña
Nacionalidad: Britanica

Thomas Daniel HEIGHTMAN,
GlaxoSmithkline, New Forntiers
Science Park South,
Third Avenue, Harlow Essex CM19 5AW
Gran Bretaña
Nacionalidad: Britanica

David Nigel HURST,
GlaxoSmithkline, New Forntiers
Science Park South,
Third Avenue, Harlow Essex CM19 5AW
Gran Bretaña
Nacionalidad: Britanica

Christopher Norbert JOHNSON,
GlaxoSmithkline, New Forntiers
Science Park South,
Third Avenue, Harlow Essex CM19 5AW
Gran Bretaña
Nacionalidad: Britanica

John SKIDMORE,
GlaxoSmithkline, New Forntiers
Science Park South,
Third Avenue, Harlow Essex CM19 5AW
Gran Bretaña
Nacionalidad: Britanica

Ian David WALL,
GlaxoSmithkline, New Forntiers
Science Park South,
Third Avenue, Harlow Essex CM19 5AW
Gran Bretaña
Nacionalidad: Britanica

Jason WITHERINGTON,
GlaxoSmithkline, Gunnels
Wood Road, Stevenage Hertfordshire
SG1 2NY
Gran Bretaña
Nacionalidad: Britanica

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 49,667
FECHA : JUNIO 21 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-074455- -00000-0000
Fecha: 2010-06-21 16:58:04 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 359

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAG	Vr. PAGO
CLARTE PARISIEK	CONSIGNACION	BANCO DE BOGOTA	062754387	174655286	21/06/2010	7,858,000.00

**** C O N C E P T O ****

CANT.	PENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES 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._____

6

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

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 CASTR
Traductor e Intérprete Ofi
Inglés - Español - Inglé
Resolución No. 2117 del 7 O

7

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 constituída 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 debiday suficientemente 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 ece de agosto del año dos mil tres.

JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra

SCRIVENER NOTARIES

DE PINNA
35 Piccadilly London W1J OLJ
Telephone:+44 (0)20 7208 2900 Facsimile: +44 (0)20 7208 0066 DX No. 48521 Piccadilly 2

8

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 / a été signé par **James Kerr Milligan**

3. Acting in the capacity of / agissant en qualité de **Notary Public**

4. Bears the seal/stamp of / est revêtu du sceau/timbre de **The Said Notary Public**

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**

FOREIGN AND COMMONWEALTH OFFICE
LONDON

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

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

OLARTERAISBECK
OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
Fax: +57-1 638-6201

www.olarteraisbeck.com

Power of Attorney

The undersigned,

Glaxo Group Limited

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

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

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

(19) World Intellectual Property Organization
International Bureau

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

PCT

(10) International Publication Number
WO 2009/080725 A1

(51) International Patent Classification:
C07D 413/04 (2006.01) *C07D 271/06* (2006.01)
C07D 413/14 (2006.01) *A61P 37/00* (2006.01)
C07D 223/16 (2006.01) *A61P 17/00* (2006.01)
C07D 267/14 (2006.01) *A61K 31/55* (2006.01)

(21) International Application Number:
PCT/EP2008/067965

(22) International Filing Date:
19 December 2008 (19.12.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0725120.0 21 December 2007 (21.12.2007) GB
0821918.0 1 December 2008 (01.12.2008) 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

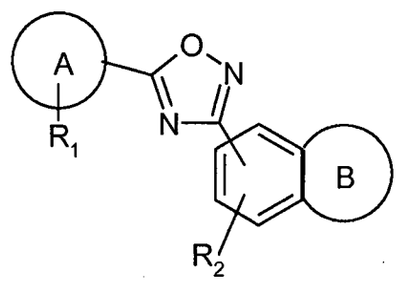
(75) Inventors/Applicants *(for US only)*: **DEMONT, Emmanuel, Hubert** [FR/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). **HEER, Jag, Paul** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **HEIGHTMAN, Thomas, Daniel** [GB/GB]; c/o GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **HURST, David, Nigel** [GB/GB]; c/o GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **JOHNSON, Christopher, Norbert** [GB/GB]; c/o GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **SKIDMORE, John** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **WALL, Ian, David** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **WITHERINGTON, Jason** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB).

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

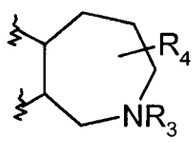
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, 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.

[Continued on next page]

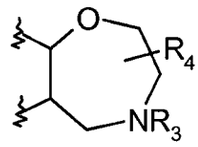
(54) Title: OXADIAZOLE DERIVATIVES ACTIVE ON SPHINGOSINE-1-PHOSPHATE (SIP)



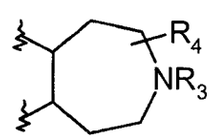
(I)



(a)



(b)



(c)

(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; R_1 is up to two substituents independently selected from halogen, $C_{(1-3)}$alkoxy, $C_{(1-3)}$flyoroalkyl, cyano, optionally substituted phenyl. $C_{(1-3)}$fluoroalkoxy. $C_{(1-6)}$alkyl and $C_{(3-6)}$Cyctoalkyl; R_2 is hydrogen, halogen or $C_{(1-4)}$alkyl; B is a 7 membered saturated ring selected from the following: Formulae (a) (b) (c) R_3 is hydrogen or $(CH_2)_{1-4}MCO_2H$; R_4 is hydrogen or $C_{(1-3)}$alkyl optionally interrupted by oxygen;

WO 2009/080725 A1

(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*

Box No. VIII(ii) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT
The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VIII, VIII(I) to (v) (in general and the specific Notes to Box No. VIII(ii). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51*bis*.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

GLAXO GROUP LIMITED is entitled to apply for and be granted a patent by virtue of the following:

(i) transfer of entitlement from inventors ***Emmanuel Hubert DEMONT, Jag Paul HEER, Thomas Daniel HEIGHTMAN, David Nigel HURST, Christopher Norbert JOHNSON, John SKIDMORE, Ian David WALL and Jason WITHERINGTON*** to GlaxoSmithKline Services Unlimited by way of employment contract

(ii) an assignment from GlaxoSmithKline Services Unlimited to Glaxo Group Limited effective 21 December 2007

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII(ii)".

activity, processes for their preparation, pharmaceutical compositions containing them and their use in the treatment of various disorders.

13

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 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 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 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 Encephalomelitis (EAE) models of MS, to reduce the severity of the induced disease (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 organs such as the lymph nodes, inducing a reversible peripheral lymphopoenia in animal models (Chiba et al 1998, J Immunology 160:5037, Forrest et al 2004 J

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 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 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 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 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 Encephalomelitis (EAE) models of MS, to reduce the severity of the induced disease (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 organs such as the lymph nodes, inducing a reversible peripheral lymphopoenia 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 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 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 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 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 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 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 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-

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)

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.

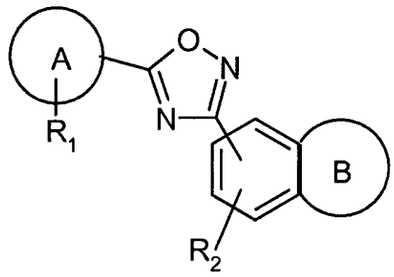
The following patent applications describe oxadiazole derivatives as S1P1 agonists: WO03/105771, WO05/058848, WO06/047195, WO06/100633, WO06/115188, WO06/131336, WO07/024922 and WO07/116866.

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

WO08/064377 describes benzocycloheptyl analogs having S1P1 receptor activity.

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

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



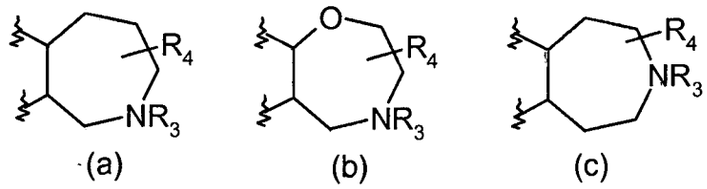
(I)

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

R_1 is up to two substituents independently selected from halogen, $C_{(1-3)}$alkoxy, $C_{(1-3)}$fluoroalkyl, cyano, optionally substituted phenyl, $C_{(1-3)}$fluoroalkoxy, $C_{(1-6)}$alkyl and $C_{(3-6)}$cycloalkyl;

R_2 is hydrogen, halogen or $C_{(1-4)}$alkyl;

B is a 7-membered saturated ring selected from the following:



(a) (b) (c)

R_3 is hydrogen or $(CH_2)_{1-4}CO_2H$;

R_4 is hydrogen or $C_{(1-3)}$alkyl optionally interrupted by oxygen;

In one embodiment of the invention,

A is phenyl;

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

R_2 is hydrogen;

B is (a);

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

R_4 is hydrogen.

In one embodiment of the invention,

A is phenyl or pyridinyl;

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

R_2 is hydrogen;

B is (b);

R_3 is hydrogen or $(CH_2)_{1-4}CO_2H$;

R_4 is hydrogen.

In one embodiment of the invention,

A is phenyl or pyridinyl;

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

R_2 is hydrogen;

B is (c);

R_3 is hydrogen 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.

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 or R_1 is chloro at the 5-position and isopropoxy at the 6-position when A is pyridinyl. 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 or R_1 is chloro at the 5-position and isopropoxy at the 6-position when A is pyridinyl.

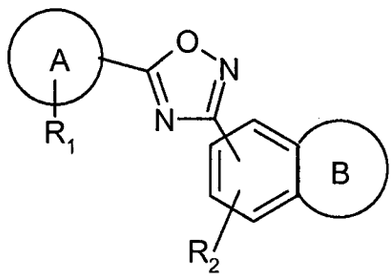
In one embodiment R_2 is hydrogen.

In one embodiment B is (b). In another embodiment B is (c).

In one embodiment R_3 is $(CH_2)_{1-3}CO_2H$. In another embodiment R_3 is $(CH_2)_3CO_2H$.

In one embodiment R_4 is hydrogen.

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



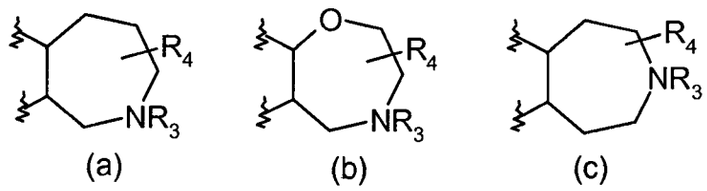
(IA)

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

R_1 is up to two substituents independently selected from halogen, $C_{(1-3)}$alkoxy, $C_{(1-3)}$fluoroalkyl, cyano, optionally substituted phenyl, $C_{(1-3)}$fluoroalkoxy, $C_{(1-6)}$alkyl and $C_{(3-6)}$cycloalkyl;

R_2 is hydrogen, halogen or $C_{(1-4)}$alkyl;

B is a 7-membered saturated ring selected from the following:



(a) (b) (c)

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

R_4 is hydrogen or $C_{(1-3)}$alkyl optionally interrupted by oxygen;

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

R_2 is hydrogen; and/or

B is (a); and/or

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

R_4 is hydrogen.

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

(19) World Intellectual Property Organization
International Bureau

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

PCT

(10) International Publication Number
WO 2009/080725 A1

(51) International Patent Classification:
C07D 413/04 (2006.01) *C07D 271/06* (2006.01)
C07D 413/14 (2006.01) *A61P 37/00* (2006.01)
C07D 223/16 (2006.01) *A61P 17/00* (2006.01)
C07D 267/14 (2006.01) *A61K 31/55* (2006.01)

(21) International Application Number:
PCT/EP2008/067965

(22) International Filing Date:
19 December 2008 (19.12.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0725120.0 21 December 2007 (21.12.2007) GB
0821918.0 1 December 2008 (01.12.2008) 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

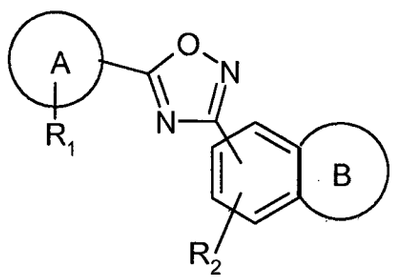
(75) Inventors/Applicants *(for US only)*: **DEMONT, Emmanuel, Hubert** [FR/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). **HEER, Jag, Paul** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **HEIGHTMAN, Thomas, Daniel** [GB/GB]; c/o GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **HURST, David, Nigel** [GB/GB]; c/o GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **JOHNSON, Christopher, Norbert** [GB/GB]; c/o GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **SKIDMORE, John** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **WALL, Ian, David** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow Essex CM19 5AW (GB). **WITHERINGTON, Jason** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB).

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

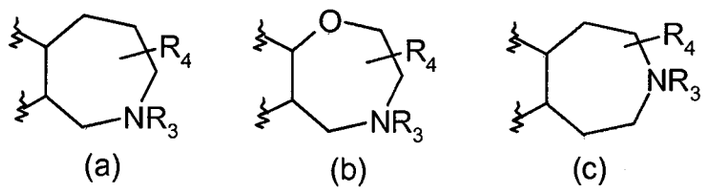
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, 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.

[Continued on next page]

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



(I)



(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; R_1 is up to two substituents independently selected from halogen, $C_{(1-3)}$alkoxy, $C_{(1-3)}$flyoroalkyl, cyano, optionally substituted phenyl. $C_{(1-3)}$fluoroalkoxy. $C_{(1-6)}$alkyl and $C_{(3-6)}$Cyctoalkyl; R_2 is hydrogen, halogen or $C_{(1-4)}$alkyl; B is a 7 membered saturated ring selected from the following: Formulae (a) (b) (c) R_3 is hydrogen or $(CH_2)_{1-4}MCO_2H$; R_4 is hydrogen or $C_{(1-3)}$alkyl optionally interrupted by oxygen;

WO 2009/080725 A1

(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*

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 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 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 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 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 Encephalomelitis (EAE) models of MS, to reduce the severity of the induced disease (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 organs such as the lymph nodes, inducing a reversible peripheral lymphopoenia 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 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 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 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 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 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 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 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-

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)

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.

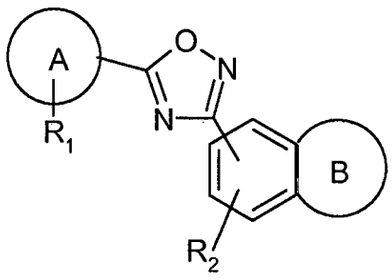
The following patent applications describe oxadiazole derivatives as S1P1 agonists: WO03/105771, WO05/058848, WO06/047195, WO06/100633, WO06/115188, WO06/131336, WO07/024922 and WO07/116866.

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

WO08/064377 describes benzocycloheptyl analogs having S1P1 receptor activity.

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

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



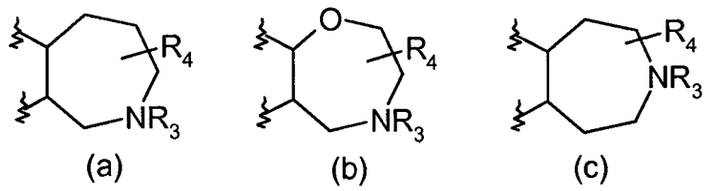
(I)

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

R_1 is up to two substituents independently selected from halogen, $C_{(1-3)}$alkoxy, $C_{(1-3)}$fluoroalkyl, cyano, optionally substituted phenyl, $C_{(1-3)}$fluoroalkoxy, $C_{(1-6)}$alkyl and $C_{(3-6)}$cycloalkyl;

R_2 is hydrogen, halogen or $C_{(1-4)}$alkyl;

B is a 7-membered saturated ring selected from the following:



(a) (b) (c)

R_3 is hydrogen or $(CH_2)_{1-4}CO_2H$;

R_4 is hydrogen or $C_{(1-3)}$alkyl optionally interrupted by oxygen;

In one embodiment of the invention,

A is phenyl;

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

R_2 is hydrogen;

B is (a);

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

R_4 is hydrogen.

In one embodiment of the invention,

A is phenyl or pyridinyl;

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

R_2 is hydrogen;

B is (b);

R_3 is hydrogen or $(CH_2)_{1-4}CO_2H$;

R_4 is hydrogen.

In one embodiment of the invention,

A is phenyl or pyridinyl;

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

R_2 is hydrogen;

B is (c);

R_3 is hydrogen 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.

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 or R_1 is chloro at the 5-position and isopropoxy at the 6-position when A is pyridinyl. 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 or R_1 is chloro at the 5-position and isopropoxy at the 6-position when A is pyridinyl.

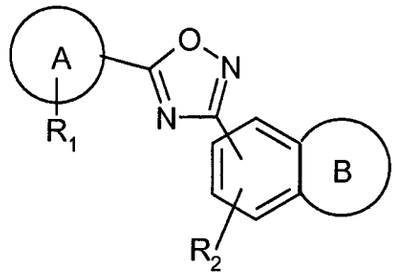
In one embodiment R_2 is hydrogen.

In one embodiment B is (b). In another embodiment B is (c).

In one embodiment R_3 is $(CH_2)_{1-3}CO_2H$. In another embodiment R_3 is $(CH_2)_3CO_2H$.

In one embodiment R_4 is hydrogen.

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



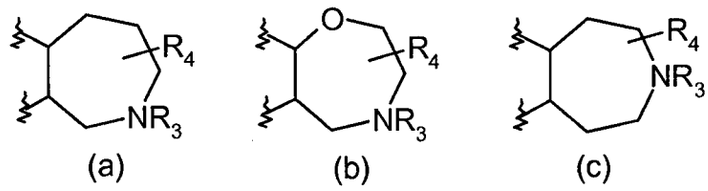
(IA)

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

R_1 is up to two substituents independently selected from halogen, $C_{(1-3)}$alkoxy, $C_{(1-3)}$fluoroalkyl, cyano, optionally substituted phenyl, $C_{(1-3)}$fluoroalkoxy, $C_{(1-6)}$alkyl and $C_{(3-6)}$cycloalkyl;

R_2 is hydrogen, halogen or $C_{(1-4)}$alkyl;

B is a 7-membered saturated ring selected from the following:



(a) (b) (c)

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

R_4 is hydrogen or $C_{(1-3)}$alkyl optionally interrupted by oxygen;

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

R_2 is hydrogen; and/or

B is (a); and/or

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

R_4 is hydrogen.

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

R_2 is hydrogen; and/or

B is (b); and/or

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

R_4 is hydrogen.

In one embodiment of the invention,

A is phenyl; and/or

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

R_2 is hydrogen; and/or

B is (c); and/or

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

R_4 is hydrogen.

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, ethoxy, propoxy, *iso*-propoxy, butoxy, *iso*-butoxy, *sec*-butoxy and *tert*-butoxy.

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

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 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.

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 stereoisomeric forms may be separated or resolved one from the other by 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.

Suitable compounds of the invention are:

7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1H-2-benzazepine

[7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]acetic acid

2-[(1-methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1H-2-benzazepin-7-yl)-1,2,4-oxadiazol-5-yl]benzonitrile

[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]acetic acid

4-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]butanoic acid

3-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]propanoic acid

2-[(1-methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1H-3-benzazepin-6-yl)-1,2,4-oxadiazol-5-yl]benzonitrile

6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1H-3-benzazepine

3-[6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]propanoic acid

[6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]acetic acid

6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1H-2-benzazepine

[6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]acetic acid

8-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine

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

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

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

7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1H-3-benzazepine

2-[(1-methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1,2,4-oxadiazol-5-yl]benzonitrile

7-{5-[4-[(1-methylethyl)oxy]-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-2,3,4,5-tetrahydro-1H-3-benzazepine

7-{5-[2-(trifluoromethyl)-4-biphenylyl]-1,2,4-oxadiazol-3-yl}-2,3,4,5-tetrahydro-1H-3-benzazepine

3-[7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]propanoic acid

[7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]acetic acid

[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]acetic acid

(7-{5-[4-[(1-methylethyl)oxy]-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)acetic acid

(7-{5-[2-(trifluoromethyl)-4-biphenylyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)acetic acid

4-[7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

4-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

4-(7-{5-[4-[(1-methylethyl)oxy]-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)butanoic acid

4-(7-{5-[2-(trifluoromethyl)-4-biphenylyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)butanoic acid

2-(Methyloxy)-5-[3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1,2,4-oxadiazol-5-yl]benzonitrile

9-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine

2-[(1-methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1,4-benzoxazepin-9-yl)-1,2,4-oxadiazol-5-yl]benzonitrile

4-[9-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]butanoic acid

4-[9-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]butanoic acid

2-[(1-methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1,2,4-oxadiazol-5-yl]benzonitrile

7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrochloride

3-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propanoic acid

3-[7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propanoic acid

4-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]butanoic acid

4-[7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]butanoic acid

2-[(1-methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1,4-benzoxazepin-8-yl)-1,2,4-oxadiazol-5-yl]benzonitrile

4-[8-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]butanoic acid

5-[9-(5-{3-Cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]pentanoic acid

[9-(5-{3-Cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]acetic acid

3-[9-(5-{5-Chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propanoic acid

3-[9-(5-{3-Cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propanoic acid

3-[9-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propanoic acid

2-[(1-Methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1,2,4-oxadiazol-5-yl]-3-pyridinecarbonitrile formate

7-(5-{5-Chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride

4-[7-(5-{5-Chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

or pharmaceutically acceptable salts thereof.

In one embodiment of the invention a compound of formula (I) is 4-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid or a pharmaceutically acceptable salt thereof.

In another embodiment of the invention a compound of formula (I) is 4-[9-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]butanoic acid or a pharmaceutically acceptable salt 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,

35

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, 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 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.

Pharmaceutically acceptable acid 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.

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 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).

The potencies and efficacies of the compounds of this invention for the S1P1 receptor can be determined by GTPγS 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.

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 erythematosis, 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 erythematosis.

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 erythematosis, psoriasis, ischemia-reperfusion injury, solid tumours, and tumour metastasis, diseases associated with angiogenesis, vascular diseases, pain

37

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 erythematosis.

Compounds of formula (I) and their pharmaceutically acceptable salts are of use as 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.

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 diseases, chronic inflammatory disorders, asthma, inflammatory neuropathies, arthritis, transplantation, Crohn's disease, ulcerative colitis, lupus erythematosis, 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, 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 erythematosis, 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 psoriasis, 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 multiple sclerosis, 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 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.

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 erythematosis, 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 in the manufacture of a medicament for use in the treatment of lupus erythematosis.

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.

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 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.

In a further aspect, the present invention provides a process for preparing a pharmaceutical composition, the process comprising mixing a compound of formula

39

(I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

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.

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); tabletting 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.

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

46

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, 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.

41

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).

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.

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 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.

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

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

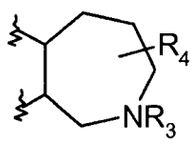
42

hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, iodine, and chlorine, such as ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{123}I and ^{125}I.

Compounds of the present invention and pharmaceutically acceptable saltss 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 of the present invention, for example those into which radioactive isotopes such as ^{3}H, ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^{8}F 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., ^{2}H, 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 preparation of a compound of formula (I).

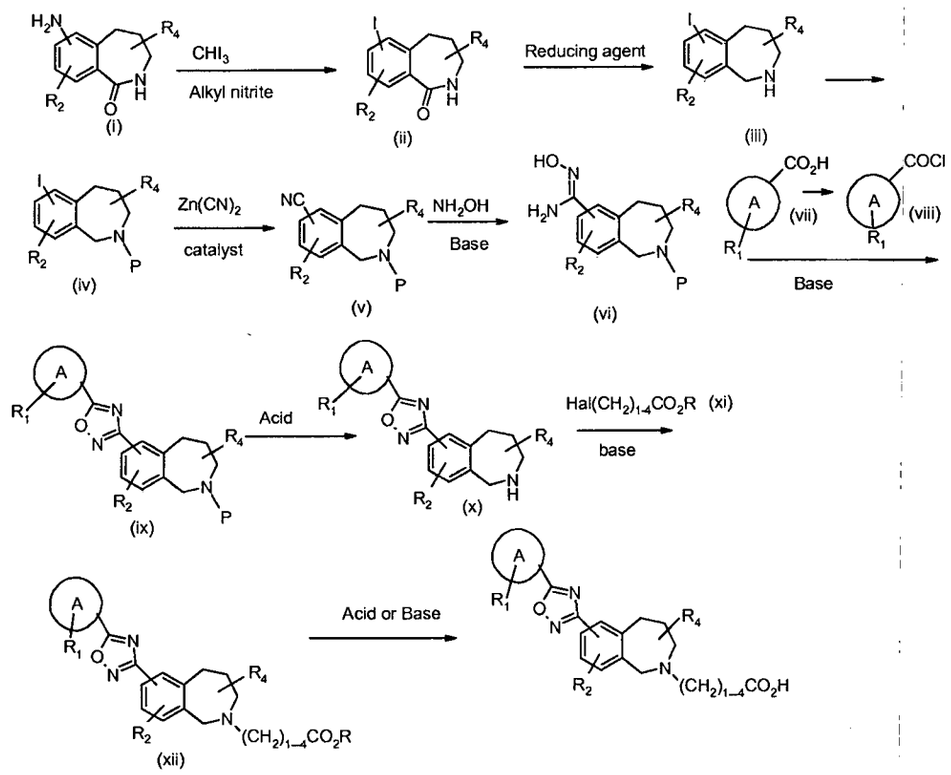
One route which may be used to prepare compounds of formula (I) when B is



(a)

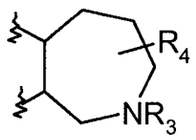
is illustrated in Scheme 1 wherein R_1,R_2 R_4 and A are as described in formula (I) except that R_2 is not chloro, bromo or iodo, R is alkyl (for example, ethyl, t-butyl) and hal is chloro, bromo or iodo.

Scheme 1



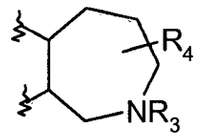
Compounds of formula (i) which are commercially available or may be prepared by a number of routes (e.g Johnson, Paul D.; *et al*; Bioorganic & Medicinal Chemistry Letters (2003), 13(23), 4197-4200), may be converted into compounds of formula (ii) by treatment with iodoform in the presence of a suitable nitrite such as tert-butyl nitrite in a suitable solvent such as tetrahydrofuran (THF). Compounds of formula (ii) may be converted into compounds of formula (iii) by treatment with an appropriate reducing agent such as diborane or lithium aluminium hydride in a solvent such as THF at an elevated temperature such as 80 °C. Compounds of formula (iii) may be converted to a protected derivative (iv), where P represents a suitable protecting group such as t-butyloxy carbonyl (BOC), for example by treatment with bis(1,1-dimethylethyl) dicarbonate in the presence of a base such as triethylamine in a suitable solvent such as dichloromethane (DCM). Compounds of formula (iv) may be converted into compounds of formula (v) by treatment with a suitable cyanide source such as zinc cyanide in the presence of a catalyst such as tetrakistriphenylphosphine palladium (0) in a suitable solvent such as dimethylformamide (DMF) at an elevated temperature such as 80 °C. Compounds of formula (v) may be converted into compounds of formula (vi) by treatment with hydroxylamine hydrochloride and an appropriate base, such as sodium bicarbonate, in a solvent such as methanol or ethanol at an elevated temperature such as 60 °C. Compounds of formula (vi) may

be converted into compounds of formula (ix) by treatment with a carboxylic acid chloride of formula (viii) in the presence of a base such as triethylamine in a suitable solvent such as DMF. Such reactions are typically stirred for a period of time at room temperature, then at elevated temperatures, such as 120 °C. Acid chlorides of formula (viii) are either commercially available or may be prepared from the corresponding acid (vii) by conventional means. Alternatively compounds of formula (vi) may be converted into compounds of formula (ix) by treatment with a carboxylic acid of formula (vii) in the presence of a suitable amide coupling agent such as 1-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDAC) and 1-hydroxybenzotriazole (HOBT) in a suitable solvent such as DMF. Such reactions are typically carried out at elevated temperature, such as 50-80 °C. Typically, the acid (vii), EDAC and HOBt are stirred for a period of time at room temperature prior to addition of the compound of formula (vi). Compounds of formula (ix), where P=BOC, may be converted into compounds of formula (x) by treatment with a suitable acid, typically trifluoroacetic acid or hydrochloric acid in a suitable solvent such as 1,4-dioxane. Compounds of formula (x) may be converted into compounds of formula (xii) by treatment with an alkylating agent (xi) in the presence of a base such as cesium carbonate in a solvent such as DMF or acetonitrile. Such reactions may be carried out at elevated temperature, such as 70 °C. The alkylating agents (xi) are typically commercially available or may be prepared using standard methods. Compounds of formula (xii) may be converted into certain compounds of formula (I) wherein B is



(a) and R_3 represents $(CH_2)_{1-4}CO_2H$ by treatment with a base such as aqueous sodium hydroxide in an alcoholic solvent such as ethanol or methanol. A co-solvent, such as THF, may be added to aid dissolution. The hydrolysis reaction may be carried out at room temperature or at an elevated temperature such as 50-80 °C. Alternatively, this transformation may be carried out using solid sodium hydroxide in ethanol in a microwave reactor at a temperature such as 100 °C or where R=t-butyl, with trifluoroacetic acid (TFA) or HCl.

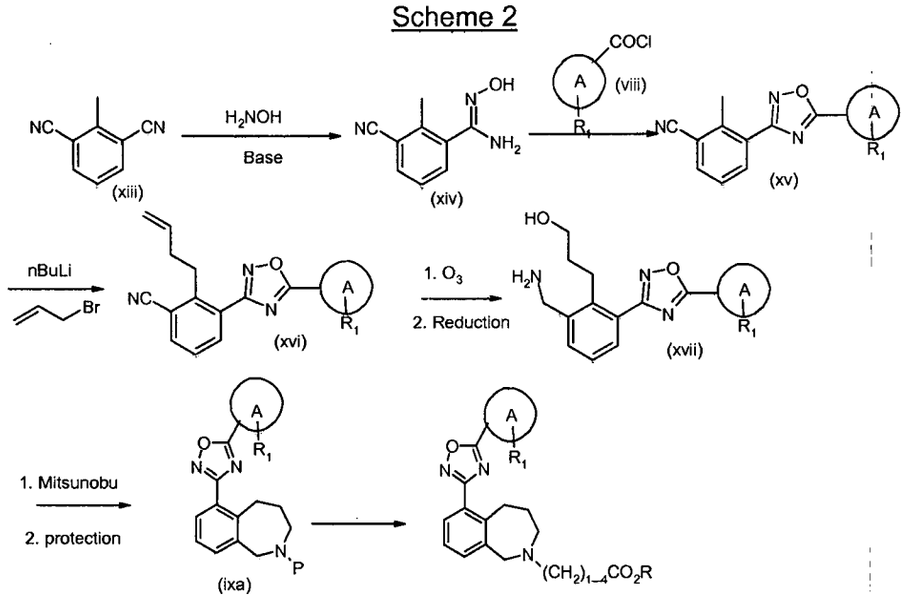
Compounds of formula (I) wherein R_2 and R_4 are both hydrogen, B is



(a)

R_3 is $(CH_2)_{1-4}CO_2H$, R_1, and A are as defined in formula (I) and the oxadiazole moiety is attached to the benzazepine moiety at position 6 may alternatively be prepared by the route illustrated in Scheme 2.

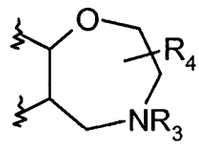
Scheme 2



The commercially available compound of formula (xiii) may be converted into the compound of formula (xiv) by treatment with hydroxylamine hydrochloride as described in Scheme 1 for conversion of (v) to (vi). The compounds of formula (xiv) may be converted into compounds of formula (xv) by treatment with a carboxylic acid chloride of formula (viii) in the presence of a base such as triethylamine as described in Scheme 1 for conversion of (vi) to (ix). Compounds of formula (xv) may be converted into compounds of formula (xvi) by treatment with an appropriate base such as n-butyl lithium followed by allyl bromide in a solvent such as THF at reduced temperatures such as -78 °C. Compounds of formula (xvi) may be converted to compounds of formula (xvii) by treatment with ozone in a suitable solvent such as DCM, at a reduced temperature such as -78°C followed by reduction using a suitable reducing agent such as borane – dimethyl sulphide complex in a suitable solvent such as THF. Compounds of formula (xvii) may be converted into compounds of formula (ix), typically by cyclisation under Mitsunobu conditions for example using

diisopropyl azodicarboxylate (DIAD) and triphenylphosphine in a suitable solvent such as DCM, followed by encorporation of a suitable protecting group on the benzazepine nitrogen, such as BOC, as described in Scheme 1 for conversion of (iii) to (iv). Compounds of formula (ixa) may be converted to compounds of formula (I) as described in scheme 1 for conversion of (ix) to certain compounds of formula (I)

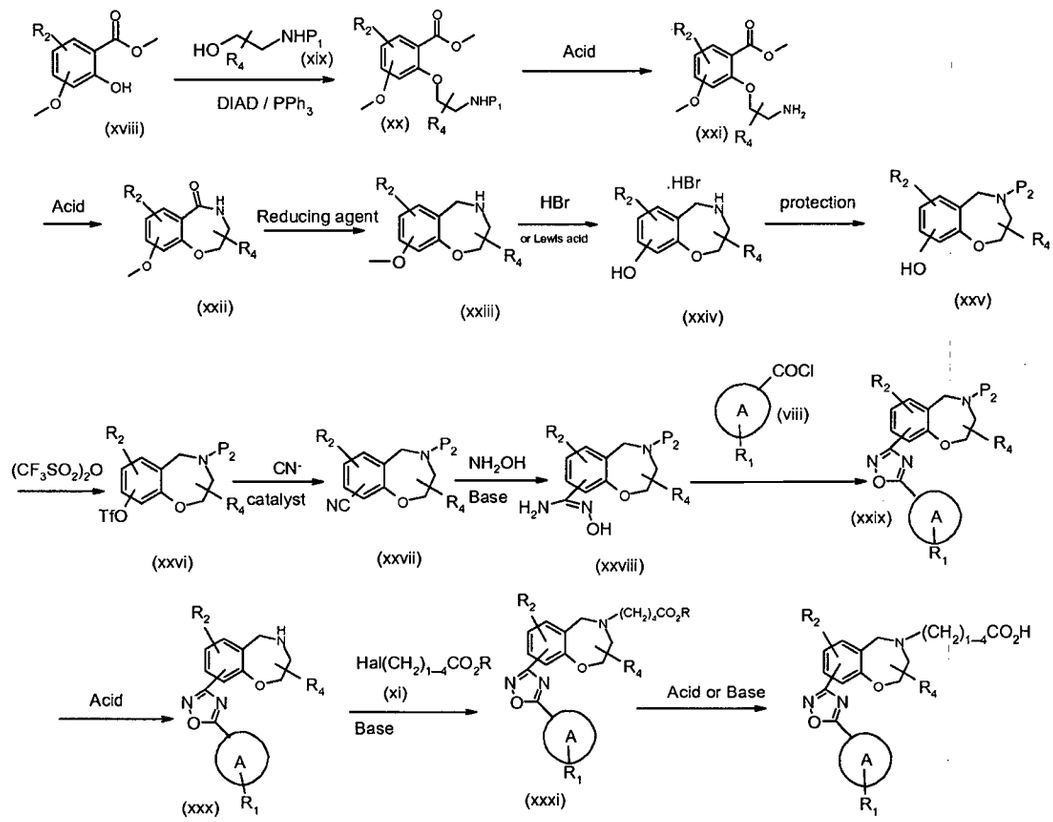
One route which may be used to prepare compounds of formula (I) wherein B is



(b)

R_3 is $(CH_2)_{1-4}CO_2H$, R_1, R_2, R_4 and A are as defined in formula (I) except that R_2 is not chloro, bromo or iodo, R is alkyl (for example methyl, t-butyl) and Hal is chloro, bromo or iodo.

Scheme 3



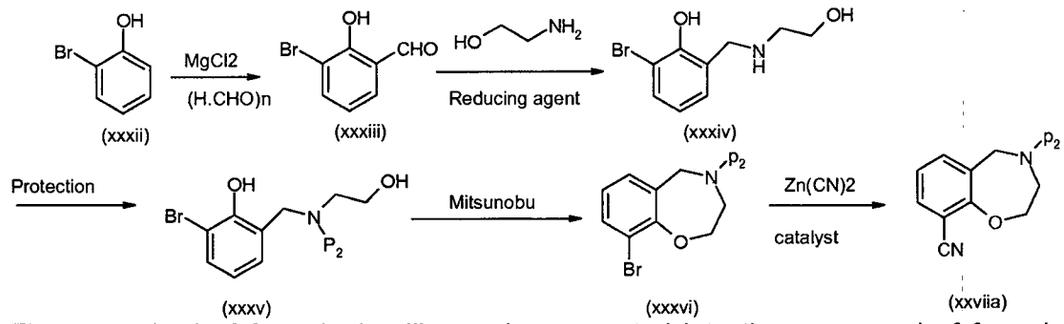
Compounds of formula (xviii) which are either commercially available (e.g. Aldrich) or prepared using standard methods, may be converted into compounds of formula

(xx), typically by reaction with a protected ethanolamine (xix) where P_1 represents a suitable protecting group such as BOC, under Mitsunobu conditions using, for example DIAD and triphenylphosphine in a suitable solvent such as THF. Compounds of formula (xx) may be converted into compounds of formula (xxi) and /or (xxii) by treatment with acid, typically trifluoroacetic acid or hydrochloric acid. Compounds of formula (xxi) may be also be converted into compounds of formula (xxii) by heating in an appropriate solvent such as toluene at elevated temperatures such as 80°C. Compounds of formula (xxii) may be converted into compounds of formula (xxiii) by treatment with an appropriate reducing agent such as lithium aluminium hydride at a low temperature such as below 15°C, in a solvent such as THF, then elevating the temperature for example to 80 °C. Compounds of formula (xxiii) may be converted to compounds of formula (xxiv) by treatment with a Lewis acid such as boron tribromide or a strong acid such as HBr.

Compounds of formula (xxiv) may be converted to a protected derivative (xxv), where P_2 represents a suitable protecting group such as t-butyloxy carbonyl (BOC), as described in Scheme 1 for conversion of (iii) to (iv). Compounds of formula (xxv) may be converted into compounds of formula (xxvi) by treatment with trifluoromethanesulphonic anhydride in an appropriate solvent such as pyridine. Compounds of formula (xxvi) may be converted into compounds of formula (xxvii) by treatment with a suitable cyanide such as zinc cyanide in the presence of a catalyst such as tetrakistriphenylphosphine palladium (0) in a suitable solvent such as DMF. Compounds of formula (xxvii) may be converted into compounds of formula (I) using methods analogous to those described for conversion of compounds of formula (v) to certain compounds of formula (I) (Scheme 1)

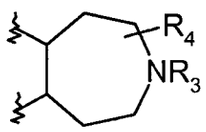
An alternative route to intermediate (xxvii) where the cyano group is in the 9 position and P_2 represents a suitable protecting group such as BOC, and R_2 and R_4 are hydrogen (represented by formula (xxviia) is illustrated in Scheme 4

Scheme 4



The compound of formula (xxxii) may be converted into the compound of formula (xxxiii) by treatment with paraformaldehyde and dry magnesium chloride in an appropriate solvent such as THF with heating under reflux. Compounds of formula (xxxiii) may be converted into compounds of formula (xxxiv) by treatment with ethanolamine in the presence of a reducing agent such as sodium triacetoxyborohydride. Compounds of formula (xxxiv) may be converted to a protected derivative (xxxv), where P_2 represents a suitable protecting group such as BOC as described in Scheme 1 for conversion (iii) to (iv). Compounds of formula (xxxv) may be converted into compounds of formula (xxxvi), typically by cyclisation under Mitsunobu conditions using, for example diisopropyl azodicarboxylate (DIAD) and triphenylphosphine in a suitable solvent such as THF. Compounds of formula (xxxvi) may be converted into compounds of formula (xxviia) by treatment with a suitable cyanide source such as zinc cyanide as described in Scheme 1 for conversion of (iv) to (v).

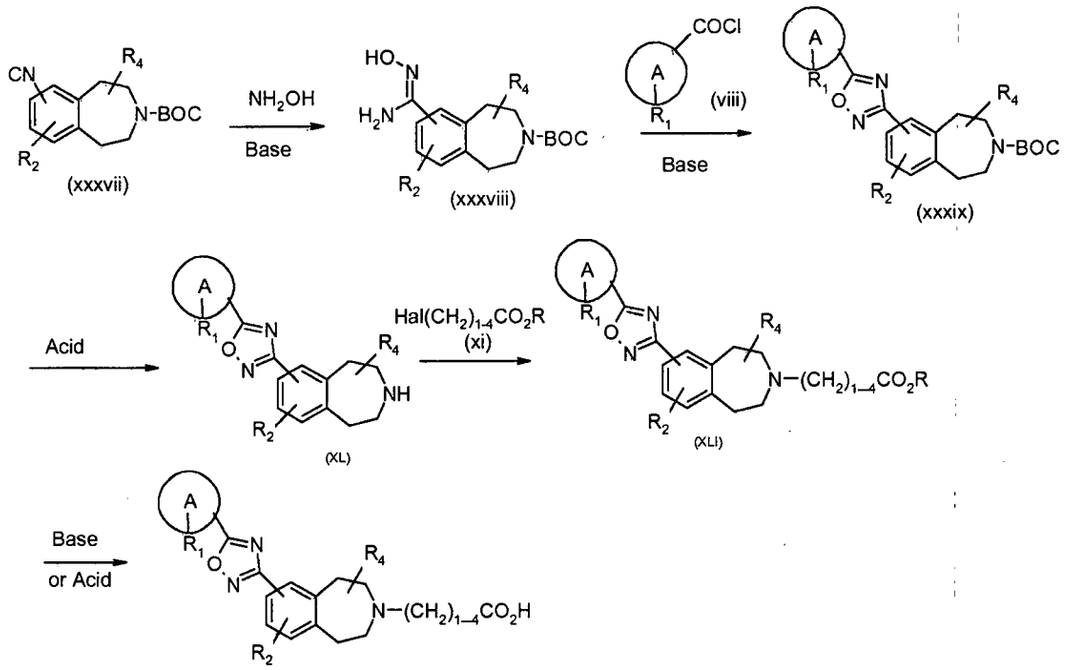
One route which may be used to prepare compounds of formula (I), wherein R_1, R_2, R_4 and A are as described in formula (I), R_3 represents $(CH_2)_{1-4}CO_2H$ and B is



(c)

is illustrated in Scheme 5. R is alkyl (for example ethyl, t-butyl) and Hal is chloro, bromo or iodo.

Scheme 5



Compounds of formula (xxxvii) for example whereby the cyano group is in the 7 position (prepared for example, using the method described in Micheli, F. *et al.* Journal of Medicinal Chemistry (2007), 50(21), 5076-5089), may be converted into compounds of formula (I) using methods analogous to those described for the conversion of compounds of formula (v) to certain compounds of formula (I) (Scheme 1)

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.

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

Abbreviations:

g –	grams
mg –	milligrams
ml –	millilitres
ul –	microlitres
BOC_2O –	bis(1,1-dimethylethyl) dicarbonate
MeCN –	acetonitrile

MeOH –	methanol
EtOH –	ethanol
Et2O –	diethyl ether
EtOAc –	ethyl acetate
DCM –	dichloromethane
DIAD –	diisopropyl azodicarboxylate
DIPEA –	diisopropylethylamine
DME –	1,2-bis(methyloxy)ethane
DMF –	N,N-dimethylformamide
DMSO –	dimethylsulphoxide
d_6DMSO–	deuterated dimethylsulphoxide
EDAC –	N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride
EDC –	N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride
EDCI –	N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride
HOBT/HOBt –	Hydroxybenzotriazole
IPA –	isopropylalcohol
MeOD –	deuterated methanol
NCS –	N-chlorosuccinimide
PPh_3 –	Triphenylphosphine
PyBOP –	Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
THF –	tetrahydrofuran
TFA -	trifluoroacetic acid
dba –	dibenzylidene acetone
RT –	room temperature
°C –	degrees Celsius
M –	Molar
H –	proton
s –	singlet
d –	doublet
t –	triplet
q –	quartet
MHz –	megahertz
MeOD –	deuterated methanol
LCMS –	Liquid Chromatography Mass Spectrometry
LC/MS –	Liquid Chromatography Mass Spectrometry
MS –	mass spectrometry

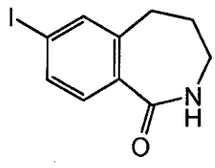
ES –	Electrospray
MH+ –	mass ion + H+
MDAP –	mass directed automated preparative liquid chromatography.
sat. –	saturated
SCX –	solid phase cation exchange chromatography

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.

Preparation 1

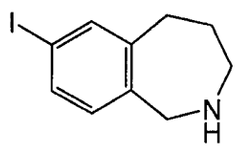
7-Iodo-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one



7-Amino-2,3,4,5-tetrahydro-1H-2-benzazepin-1-one (may be prepared as described in : *Preparation of benzazepinylpyrrolidonylsulfonamides as Factor Xa inhibitors*; WO2007059952) (500mg, 2.84 mmol) and triiodomethane (2234 mg, 5.67 mmol) were dissolved in THF (100ml). Then 1,1-dimethylethyl nitrite (0.675 ml, 5.67 mmol) dissolved in THF (20ml) was added drop-wise over 20 minutes and the resultant solution stirred for 1 hour. The mixture was heated at 50 °C for 30 minutes. Most of the solvent was removed by evaporation and the crude subjected to biotage chromatography (EtOAc/hexane 3:1) to yield the title compound (550 mg) as a pale yellow solid. MS (ES) $C_{10}H_{10}INO$ requires 287: found 287.8 $(M+H)^+$.

Preparation 2

7-Iodo-2,3,4,5-tetrahydro-1H-2-benzazepine

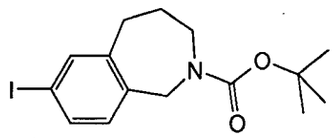


7-Iodo-2,3,4,5-tetrahydro-1H-2-benzazepin-1-one (Preparation 1) (550mg, 1.916 mmol) was dissolved in dry THF (70 ml) and treated with borane-THF complex (1M) (11.49 ml, 11.49 mmol) and heated at reflux for 4 hours. Then the reaction was left

standing overnight. Additional borane-THF complex (1M, 2 ml) was added and the reaction heated at reflux temperature for a further 2 hours and 30 minutes. Methanol was carefully added to the cooled reaction mixture. The reaction was stirred until fizzing stopped. Then 2N HCl (aq) (20ml) was carefully added portion-wise and, after fizzing had subsided, the solution heated at 75 °C for 30 minutes. LC/MS showed one major product. The reaction mixture was cooled and water was added (20ml). The mixture was washed with EtOAc (40ml), basified with 2 N NaOH(aq) and extracted with EtOAc (50ml). The EtOAc layer was dried over anhydrous $MgSO_4$ and evaporated to yield the tiltle compound (400mg) as a white solid. MS (ES) $C_{10}H_{12}IN$ requires 273: found 274 $(M+H)^+$.

Preparation 3

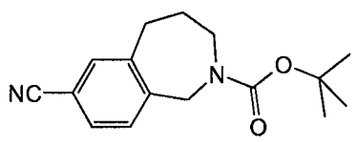
1,1-Dimethylethyl 7-iodo-1,3,4,5-tetrahydro-2H-2-benzazepine-2-carboxylate



7-Iodo-2,3,4,5-tetrahydro-1H-2-benzazepine (Preparation 2) (450mg, 1.648 mmol) was dissolved in DCM (30ml) and treated with BOC_2O (0.459 ml, 1.977 mmol) followed by triethylamine (0.459 ml, 3.30 mmol). The reaction mixture was stirred at RT for 30 minutes. LC/MS showed one major product. The reaction was washed with 0.5M HCl (20ml), sat $NaHCO_3$ (20ml), dried over anhydrous $MgSO_4$ and evaporated to yield the title compound (650 mg) as a colourless oil. MS (ES) $C_{15}H_{20}INO_2$ requires 373; found 318 $(M+H-56)^+$.

Preparation 4

1,1-Dimethylethyl 7-cyano-1,3,4,5-tetrahydro-2H-2-benzazepine-2-carboxylate



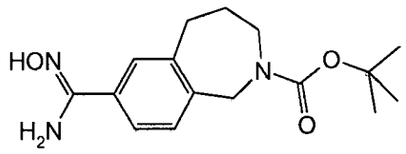
1,1-Dimethylethyl-7-iodo-1,3,4,5-tetrahydro-2H-2-benzazepine-2-carboxylate (Preparation 3) (650mg, 1.742 mmol), zinc(II)cyanide (123 mg, 1.045 mmol) and tetrakis(triphenylphosphine)palladium(0) (201 mg, 0.174 mmol) were stirred in dry DMF at 80 °C for 45 minutes. EtOAc (100ml) was added to the cooled reaction before washing with water (2x70ml) and brine (100ml). The EtOAc layer was dried over anhydrous $MgSO_4$ and evaporated. TLC (EtOAc/hexane 1:3) showed 2 spots,

53

one with a very high RF. The crude product was subjected to biotage chromatography (EtOAc/hexane 1:3) and the lower RF spot was isolated. On evaporation the title compound was obtained (350 mg) as a colourless oil. MS (ES) $C_{16}H_{20}N_2O_2$ requires 272; found 217(M+H-56)$^+$.

Preparation 5

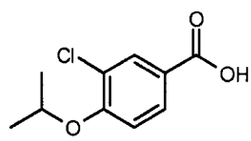
1,1-Dimethylethyl 7-[(hydroxyamino)(imino)methyl]-1,3,4,5-tetrahydro-2H-2-benzazepine-2-carboxylate



1,1-Dimethylethyl 7-cyano-1,3,4,5-tetrahydro-2H-2-benzazepine-2-carboxylate (Preparation 4) (350mg, 1.285 mmol), hydroxylamine hydrochloride (223 mg, 3.21 mmol) and sodium bicarbonate (540 mg, 6.43 mmol) were suspended in ethanol (15 ml) and stirred at 55 °C for 5 hours. The reaction mixture was left standing overnight. LC/MS showed a single major product. Inorganics were removed by filtration, washing well with 10% MeOH/DCM to dissolve any precipitated product. Solvent evaporation yielded a white solid. Trituration with ether gave the title compound (320 mg). MS (ES) $C_{16}H_{23}N_3O_3$ requires 305; found 306.2 $(M+H)^+$.

Preparation 6

3-Chloro-4-[(1-methylethyl)oxy]benzoic acid



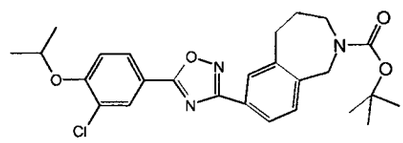
Propan-2-ol (2.45 ml) and PPh_3 (1.18 g) were dissolved in THF (30 ml), cooled to 0 °C, treated with methyl 3-chloro-4-hydroxybenzoate (6.00 g) followed by the drop-wise addition of DIAD (9.44 ml) and stirred at RT overnight. The reaction mixture was then evaporated and purified on silica cartridges (4 x 100 g), eluting with a 0 to 40 % mixture of EtOAc in pentane to give the crude product (7.00 g) as a colourless oil. This was dissolved in MeOH (30 ml) and 2 M aqueous NaOH (30 ml) and stirred at RT for a weekend. The reaction mixture was then evaporated and re-dissolved in H_2O. This solution was washed with Et_2O, acidified to pH = 1 and extracted with Et_2O. These latter extracts were dried over anhydrous $MgSO_4$, filtered and evaporated to give the title compound (4.16 g) as a white solid. δH (MeOD, 400MHz):

54

1.37 (6H, d), 4.77 (1H, septet), 7.12 (1H, d), 7.90 (1H, d), 7.98 (1H, s). MS (ES): $C_{10}H_{11}{}^{35}ClO_3$ requires 214; found 215 $(M+H)^+$.

Preparation 7

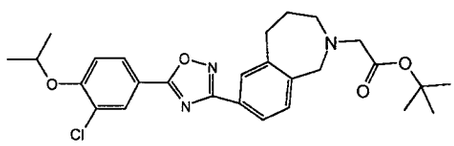
1,1-Dimethylethyl 7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepine-2-carboxylate



3-Chloro-4-[(1-methylethyl)oxy]benzoic acid (Preparation 6) (105 mg, 0.491 mmol), EDC (113 mg, 0.589 mmol) and HOBT (90 mg, 0.589 mmol) were dissolved in dry DMF (5 ml) and stirred for 5 minutes. 1,1-Dimethylethyl 7-[hydroxyamino)(imino)methyl]-1,3,4,5-tetrahydro-2H-2-benzazepine-2-carboxylate (Preparation 5) (150mg, 0.491 mmol) was added and the mixture stirred for 1 hour, heated at 90 °C for 2 hours then left standing overnight. The reaction was heated at 90 °C for a further 3 hours. EtOAc (50ml) was added and the reaction washed with sat. $NaHCO_3$ (aq) (50ml) and water (2x50ml) before drying over anhydrous $MgSO_4$ and evaporation of the solvent. The crude oil obtained was subjected biotage chromatography (EtOAc/hexane 1:4) to give 100 mg of a colourless oil. The oil slowly began to solidify overnight to a white waxy solid. Trituration with ether/hexane yielded the title compound (38 mg) as a white solid after filtration. A further batch (30mg) precipitated out of the solution slowly. δH (400 MHz, d_6DMSO) 1.31 (9H, s), 1.36 (6H, d), 1.69 (2H, m), 3.06 (2H, m), 3.65 (2H, m), 4.44 (2H, s), 4.84-4.94 (1H, m), 7.38-7.46 (2H, m), 7.84-7.91 (2H, m), 8.11 (1H, dd), 8.18 (1H, d).

Preparation 8

1,1-Dimethylethyl [7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]acetate



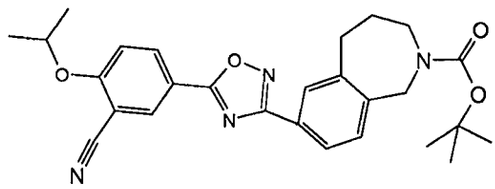
7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1H-2-benzazepine (Example 1) (60mg, 0.143 mmol) and caesium carbonate (140 mg, 0.428 mmol) were stirred in dry DMF (5 ml) and treated with tert-butyl bromoacetate (0.032 ml, 0.214 mmol). The mixture was stirred at RT for 1.5 hours.

55

EtOAc (50ml) and ether (20ml) were added and the mixture washed with water (3x 60ml) and brine (40ml). Drying over anhydrous $MgSO_4$ and evaporation of solvent yielded a clear, colourless oil (80mg). The oil was subjected to biotage chromatography (EtOAc/hexane 3:1) to give the title compound (65mg) as a clear, colourless oil. MS (ES) $C_{27}H_{32}{}^{35}ClN_3O_4$ requires 497; found 498 $(M+H)^+$.

Preparation 9

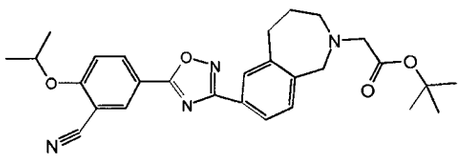
1,1-Dimethylethyl 7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepine-2-carboxylate



3-Cyano-4-[(1-methylethyl)oxy]benzoic acid (can be prepared as described in WO2005/58848) (302 mg, 1.474 mmol), EDC (339 mg, 1.768 mmol) and HOBT (271 mg, 1.768 mmol) were stirred in DMF (3 ml) for 5 minutes. 1,1-Dimethylethyl 7-[(hydroxyamino)(imino)methyl]-1,3,4,5-tetrahydro-2H-2-benzazepine-2-carboxylate (Preparation 5) (450mg, 1.474 mmol) was added and the reaction mixture stirred at RT for 1 hour. There was still some 3-cyano-4-[(1-methylethyl)oxy]benzoic acid acid present. Further quantities of EDC (100mg) and 1,1-Dimethylethyl 7-[(hydroxyamino)(imino)methyl]-1,3,4,5-tetrahydro-2H-2-benzazepine-2-carboxylate (100mg) were added and the reaction stirred for 1 hour. Then the reaction was heated at 80 °C for 3 hours and left standing overnight. The reaction was then heated at 90 °C for 1 hour. EtOAc (70ml) was added and the reaction mixture washed with sat. $NaHCO_3$ (50ml) and water (2x70ml), dried over anhydrous MgSO4 and evaporated. The crude material obtained was subjected to biotage chromatography (EtOAc/hexane 1:2)., yielding a white solid on evaporation. Trituration with ether yielded the title compound (320mg) as a white solid. NMR (400 MHz, d_6DMSO) 1.31 (9H, s), 1.38 (6H, d), 1.69 (2H, br. s), 3.06 (2H, broad s), 3.65 (2H, br. s), 4.44 (2H, s), 4.94-5.03 (1H, m), 7.38-7.43 (1H, m), 7.56 (1H, d), 7.84-7.91 (2H, m), 8.40 (1H, dd), 8.50 (1H, d)

Preparation 10

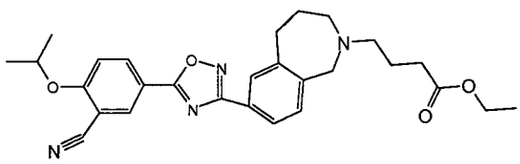
1,1-Dimethylethyl [7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]acetate



2-[(1-Methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1H-2-benzazepin-7-yl)-1,2,4-oxadiazol-5-yl]benzonitrile hydrochloride (Example 3) (70mg, 0.170 mmol) and caesium carbonate (167 mg, 0.511 mmol) in dry DMF (5ml) were treated with tert-butyl bromoacetate (0.038 ml, 0.256 mmol) and stirred at RT for 3 hours to give a single product. EtOAc (40ml) was added and the mixture washed with water (2X50ml), dried over anhydrous $MgSO_4$ and evaporated to yield the title compound (85 mg) as a clear, colourless oil. MS (ES) $C_{28}H_{32}N_4O_4$ requires 488; found 489 $(M+H)^+$.

Preparation 11

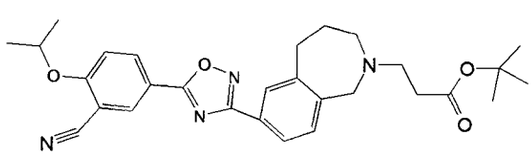
Ethyl 4-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]butanoate



2-[(1-Methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1H-2-benzazepin-7-yl)-1,2,4-oxadiazol-5-yl]benzonitrile hydrochloride (Example 3) (70mg, 0.170 mmol) and caesium carbonate (167 mg, 0.511 mmol) in dry DMF (5ml) were treated with ethyl 4-bromobutyrate (0.037 ml, 0.256 mmol) and stirred at 60 °C for 2 hours. Additional quantities of ethyl 4-bromobutyrate (37 ul) were added and the reaction heated at 60 °C for 3 hours. The reaction was left standing overnight. EtOAc (50ml) was added and the mixture washed with water (2x60ml), dried over anhydrous $MgSO_4$ and evaporated to yield the title compound (90mg) as a clear, colourless oil. MS (ES) $C_{28}H_{32}N_4O_4$ requires 488; found 489.0 $(M+H)^+$.

Preparation 12

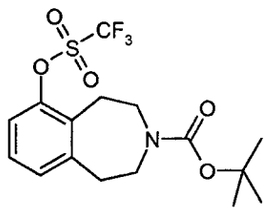
1,1-Dimethylethyl 3-[7-(5-{3-cyano-4-[(1-methylethyl)oxy] phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]propan-oate



2-[(1-Methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1H-2-benzazepin-7-yl)-1,2,4-oxadiazol-5-yl]benzonitrile hydrochloride (Example 3) (70mg, 0.170 mmol) and caesium carbonate (167 mg, 0.511 mmol) were stirred in dry DMF (5ml) and treated with 1,1-dimethylethyl 3-bromopropanoate (0.043 ml, 0.256 mmol) then stirred at 60 °C for 2 hours. Further quantities of 1,1-dimethylethyl 3-bromopropanoate (44 µl) were added and the reaction stirred at 60 °C for 3 hours. The reaction was left standing overnight. 1,1-Dimethylethyl 3-bromopropanoate (43 µl) was added and the reaction mixture stirred at 60 °C for 7 hours then left standing overnight. EtOAc (50ml) was added and the reaction mixture washed with water (2x50ml), dried over anhydrous $MgSO_4$ and evaporated to yield a clear, colourless oil (100mg). The oil slowly solidified. Trituration with ether/hexane to yielded the title compound (70 mg) as a white solid. MS (ES) $C_{29}H_{34}N_4O_4$ requires 502; found 503.0 (M+H).

Preparation 13

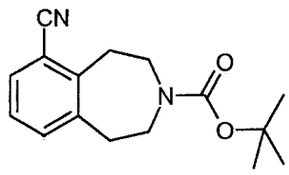
1,1-Dimethylethyl 6-{[(trifluoromethyl)sulfonyl]oxy}-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate



To a stirred solution of 1,1-dimethylethyl 6-hydroxy-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (may be prepared as described in WO2006/002928) (6.545g) in dry DCM (100 ml) under argon at -10 °C was added triethylamine (4 ml). After 10 minutes trifluoromethanesulfonic anhydride (4.7 ml) was added dropwise over 10 minutes. The colourless solution turned amber then red. The reaction was allowed to reach RT over 30 minutes then stirred at RT for 18 hours. Then the reaction was poured onto saturated sodium carbonate solution (100ml) and the DCM layer collected, dried and evaporated. The title compound (5g) was obtained by chromatography (eluting with DCM). δH (400 MHz, $CDCl_3$) 7.22-7.12 (3H, m), 3.59-3.57 (4H, m), 3.01-2.99 (4H, m), 1.48 (9H, s); MS (ES) $C_{16}H_{20}F_3NO_5S$ requires 395; found 340 $[M+H-56]^+$.

Preparation 14

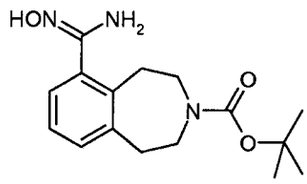
1,1-Dimethylethyl 6-cyano-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate



1,1-dimethylethyl 6-{[(trifluoromethyl)sulfonyl]oxy}-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (Preparation 13) (5g), zinc (II) cyanide (1.5g) and tetrakis(triphenylphoshine)palladium(0) (1.5g) were heated in dry DMF at 150 °C for 18 hours. The cooled reaction mixture was diluted with EtOAc (200 ml) and filtered. The filtrate was washed with saturated sodium bicarbonate, (200 ml), water (200 ml) and brine (200 ml). The crude reaction mixture was dried in the usual manner and evaporated. Purification by chromatography (eluting with DCM) yielded the title compound (3.4 g). δH (400 MHz, $CDCl_3$) 7.50 (1H, d), 7.35 (1H, d), 7.27-7.21 (1H, m), 3.62-3.56 (4H, m), 3.22-3.20 (2H, m), 2.97-2.94 (2H, m), 1.47 (9H, s); MS (ES) $C_{16}H_{20}N_2O_2$ requires 272; found 217 $[M+H-56]^+$, 273 $[M+H]^+$.

Preparation 15

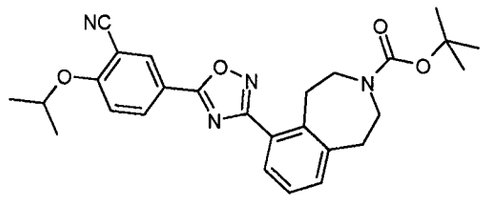
1,1-Dimethylethyl 6-[(hydroxyamino)(imino)methyl]-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate



1,1-dimethylethyl 6-cyano-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (Preparation 14) (1.15g), hydroxylamine hydrochloride (1.18g) and sodium bicarbonate (1.76g) were heated at 60 °C in ethanol (100 ml) for 18 hours under argon. The cooled reaction was evaporated to dryness, partitioned between DCM (100 ml) and water (100 ml). The DCM layer was collected and the water layer washed with DCM (50 ml). The combined DCM layers were dried and evaporated. The title compound (506 mg) was isolated by chromatography eluting with 5% methanol in DCM. δH (400 MHz, $CDCl_3$) 7.27 (1H, s) 7.16-7.13 (2H, m), 5.38 (1H, br. s), 3.58-3.55 (4H, m), 3.05 (2H, br. s), 2.89 (2H, br. s) 1.46 (2H br. s), 1.12 (9H, br. s); MS (ES) $C_{16}H_{23}N_3O_3$ requires 305; found 306 $[M+H]^+$.

Preparation 16

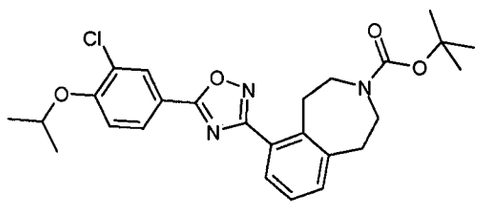
1,1-Dimethylethyl 6-(5-{3-cyano-4-[(1-methylethyl)oxy] phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate



1,1-Dimethylethyl 6-[(hydroxyamino)(imino)methyl]-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (Preparation 15) (360 mg, 1.179 mmol) was dissolved in THF (50 ml) and stirred with sodium hydride (60% dispersion in mineral oil, 51.9 mg, 1.297 mmol) under argon at room temperature for 30 minutes. Then methyl 3-cyano-4-[(1-methylethyl)oxy] benzoate (may be prepared as described in WO2005058848) (388 mg, 1.768 mmol) was added as a THF solution (5ml) 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 product was isolated by silica chromatography (eluting with DCM) to give 1,1-dimethylethyl 6-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (505 mg, 1.011 mmol, 86 % yield) as a white foam. δH (400 MHz, $CDCl_3$) 8.41 (1H, s), 8.33 (1H, dd), 7.7 (1H, dd), 7.31-7.25 (2H, m), 7.13 (1H, d), 4.80 (1H, sept), 3.63-3.62 (4H, m), 3.3-3.2 (2H, m), 2.95-3.05 (2H, m), 1.47 (6H, d), 1.43 (9H, br.s); MS (ES) $C_{27}H_{30}N_4O_4$ requires 474; found 475 $[M+H]^+$.

Preparation 17

1,1-Dimethylethyl 6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate

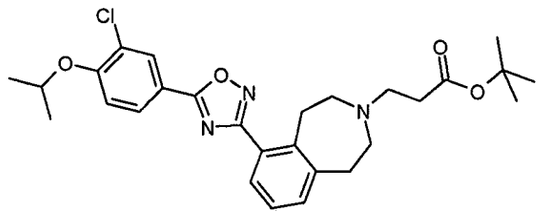


1,1-dimethylethyl 6-[(hydroxyamino)(imino)methyl]-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (Preparation 15) (170 mg, 0.557 mmol) was dissolved in THF (30 ml) and stirred with sodium hydride (24.49 mg, 0.612 mmol) under argon at room temperature for 30 minutes. Then methyl 3-chloro-4-[(1-methylethyl)oxy]benzoate (may be prepared as described in WO2005058848) (191 mg, 0.835 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 title compound was isolated by silica chromatography (eluting with DCM). 1,1-dimethylethyl 6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (260 mg, 0.537 mmol, 96 % yield) was isolated as an off-white foam. δH (400 MHz, $CDCl_3$) 8.22 (1H, s), 8.05 (1H d), 7.68 (1H, d), 7.30-7.24 (2H, m), 7.06 (1H, d), 4.72 (1H, sept), 3.65-3.55 (4H, m), 3.35-3.25 (2H, m), 2.95-3.05 (2H, m), 1.45 (6H, d), 1.43 (9H, s); MS (ES) $C_{26}H_{30}{}^{35}ClN_3O_4$ requires 483; found 484 $[M+H]^+$.

Preparation 18

1,1-Dimethylethyl 3-[6-(5-{3-chloro-4-[(1-methylethyl)oxy] phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]propan-oate

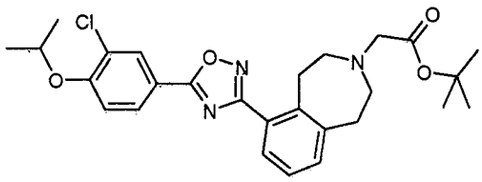


In a 5 ml microwave reaction vessel was added 6-(5-{3-chloro-4-[(1-methyl ethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1H-3-benzazepine (Free base of Example 8, obtained by standard methods e.g. partitioning between organic and basic aqueous solvents and collecting organic solvent) (70 mg) in DMF (3 ml) to give a brown solution. Then potassium carbonate (101 mg) was added followed by 1,1-dimethylethyl 3-bromopropanoate (38.1 mg, 0.182 mmol). The reaction mixture was heated at 100 °C for 10 minutes. The cooled reaction mixture was diluted with DCM (5 ml) and purified by SCX (washing with methanol and eluting the crude amino ester with methanolic ammonia). Purification by MDAP yielded the amino ester, 1,1-dimethylethyl 3-[6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]propanoate (25 mg, 0.046 mmol, 25.4 % yield) isolated as a light yellow oil. MS (ES) $C_{28}H_{34}{}^{35}ClN_3O_4$ requires 511; found 512 $[M+H]^+$.

Preparation 19

61

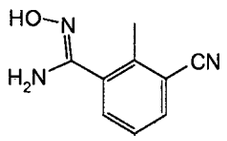
1,1-Dimethylethyl [6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]acetate



In a 5 ml microwave reaction vessel was added 6-(5-{3-chloro-4-[(1-methylethyl) oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (Example 8) (110 mg, 0.262 mmol). Then potassium carbonate (101 mg) was added followed by 1,1-dimethylethyl bromoacetate (51.0 mg, 0.262 mmol). The reaction mixture was heated at 100 °C for 10 minutes. The cooled reaction mixture was diluted with DCM (5 ml) and purified by SCX (washing with methanol and eluting the crude amino ester with methanolic ammonia). 1,1-dimethylethyl [6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]acetate (120 mg, 0.241 mmol, 92 % yield) was isolated as a pale yellow oil. MS (ES) $C_{27}H_{32}{}^{35}ClN_3O_4$ requires 497; found 498 $[M+H]^+$.

Preparation 20

3-Cyano-N-hydroxy-2-methylbenzenecarboximidamide



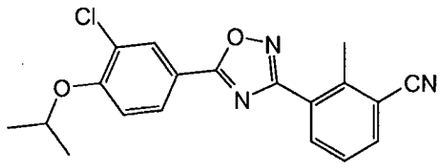
A suspension of 2,6-dicyanotoluene (25.0 g, 176 mmol), hydroxylamine hydrochloride (73.0 g, 1.06mol) and triethylamine (142 g, 1.41 mol) in chloroform (500 ml) was stirred at 50 °C for 7 h, then allowed to stand at room temperature overnight. The reaction mixture was cooled in ice, treated with 5M HCl to pH1 and extracted three times with chloroform. The aqueous was extracted with THF (x 7), cooled in ice, raised to pH4 with 40% NaOH and extracted with THF (x 3). The latter THF extracts were combined and evaporated to dryness to give a buff solid consisting of the product and approximately a third of an equivalent of triethylamine (11.0 g). ^1H NMR (400 MHz, d_4-MeOH) δ (inter alia) 7.70-7.76 (1H, m), 7.57-7.63 (1H, m), 7.35-7.62 (1H, m), 2.58 (3H, s); MS (ES) $C_9H_9N_3O$ requires 175; found 176 $[M+H]^+$. The former seven extracts of THF were combined, evaporated to dryness and dissolved in water. The aqueous solution was extracted twice with chloroform,

62

adjusted to pH4 and extracted with THF (x 3). Evaporation of the combined THF extracts gave a further 4.5 g of product.

Preparation 21

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



To a solution of 3-cyano-N-hydroxy-2-methylbenzenecarboximidamide (Preparation 20) (1.70 g, 9.70 mmol) in THF (100 ml) was added sodium hydride (0.427 g, 10.67 mmol) under argon at rt and the suspension stirred for 30 min. Then methyl 3-chloro-4-[(1-methylethyl)oxy]benzoate (may be prepared as described in WO2005058848) (3.33 g, 14.56 mmol) was added and reaction heated at reflux for 45 minutes, then cooled to RT and stirred for 3 days.

Separately, to a suspension of 3-cyano-N-hydroxy-2-methylbenzenecarboximidamide (Preparation 20) (10.48 g, 59.8 mmol) in THF (250 ml) under argon at rt was added sodium hydride (2.87 g, 71.8 mmol) portionwise and the resulting suspension stirred at RT for 30 minutes. Methyl 3-chloro-4-[(1-methylethyl)oxy]benzoate (19.9 g, 87 mmol) was added and reaction heated at reflux for 4 h, then stirred at rt for 16 h.

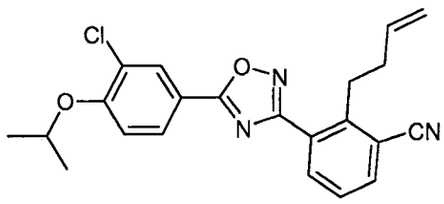
The two reaction mixtures were combined. Water (200 ml) was added then the mixture extracted with DCM (2x250 ml). The organic layers were combined, washed with brine (100 ml) and concentrated in vacuo to give a crude white solid (28.1 g). The solid was redissolved in DCM (200 ml), THF (150 ml) and EtOH (50 ml) and passed through a short plug of silica (1 cm deep). Elution with DCM followed by concentration in vacuo gave a pale yellow solid 3-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2-methylbenzonitrile (18.10 g, 51.2 mmol, 80 % yield). Elution of the silica with DCM-EtOH (2:1) followed by concentration in vacuo gave a pale yellow solid 3-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2-methylbenzonitrile (2.81 g, 6.35 mmol, 10 % yield). Both batches were analytically identical. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, d), 8.22 (1H, d), 8.05 (1H, dd), 7.77 (1H, d), 7.45 (1H, t), 7.07 (1H,

63

d), 4.73 (1H, sept), 2.90 (3H, s), 1.47 (6H, d); MS (ES) $C_{19}H_{16}{}^{35}ClN_3O_2$ requires 353; found 354 $[M+H]^+$.

Preparation 22

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

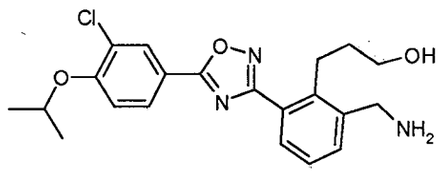


To a solution of diisopropylamine (15.15 ml, 106 mmol) in dry THF (650 m) at -78 °C under Ar was added ^{n}BuLi (44.3 ml, 70.9 mmol) down the side of the flask and the resulting solution stirred for 1 h. A solution of 3-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2-methylbenzonitrile Preparation 21) (12.54 g, 35.4 mmol) in dry THF (100 ml) under Ar was added dropwise at ~10 mlmin^{-1}, and the resulting dark blue solution stirred at -78 °C for 45 min. Allyl bromide (6.13 ml, 70.9 mmol) was added dropwise at ~3 mlmin^{-1}, and the resulting dark red solution stirred for 30 min at -78 °C. 1 M HCl(aq) (375 ml) was added, the mixture allowed to warm to RT then the layers separated. The aqueous was extracted with EtOAc (2 x 125 ml), then the combined organics washed with brine (250 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give a crude red oil (12.8 g). This was redissolved in DCM (20 ml) and added to a pre-wet (isohexane) column of silica (5 cm x 5 cm). Elution with EtOAc-isohexane (1:3) and concentration of the desired fractions gave a pale orange solid 2-(3-buten-1-yl)-3-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)benzonitrile (9.50 g, 20.98 mmol, 59.2 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (1H, d), 8.24 (1H, d), 8.05 (1H, dd), 7.79 (1H, d), 7.46 (1H, t), 7.07 (1H, d), 5.94 (1H, ddt), 5.07 (1H, dq), 5.01 (1H, dd), 4.73 (1H, sept), 3.40 (2H, t), 2.47 (2H, qd), 1.45 (6H, d); MS (ES) $C_{22}H_{20}{}^{35}ClN_3O_2$ requires 393; found 394 $[M+H]^+$.

Preparation 23

3-[2-(Aminomethyl)-6-(5-{3-chloro-4-[(1-methylethyl)oxy] phenyl}-1,2,4-oxadiazol-3-yl)phenyl]-1-propanol

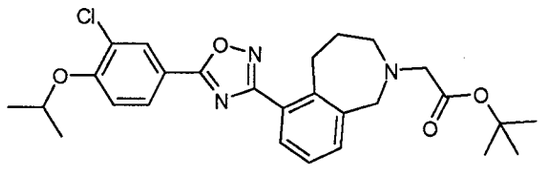
64



Through a solution of 2-(3-buten-1-yl)-3-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)benzonitrile (Preparation 22) (8.26 g, 20.97 mmol) in DCM (125 ml) under Ar at -78 °C was bubbled Ar then O_2 (5 min each). The ozonoliser (model 502; 75 lh^{-1}; 0.3 A) was switched on and the orange solution ozonolised until it had turned an opaque green-grey colour (3 hrs). The ozonoliser was switched off, and O_2, then Ar bubbled though the solution (10 min each). The solution was allowed to warm to RT under Ar, then concentrated in vacuo to give an opaque yellow oil. This was redissolved in dry THF (200 ml), BH_3.DMS (9.96 ml, 105 mmol) added (CARE: gas evolution), and the solution stirred at RT for 18 hrs and then at 40 °C for 3 hrs. The reaction was cooled to 0 °C, then 0.1M aqueous HCl (150 ml) was added cautiously (CARE: gas evolution), then allowed to stir at RT for 18 hrs. The solution was passed directly down an SCX-2 column (50 g), washing with MeOH. The product was eluted with 0.5M NH_3 in MeOH; concentration in vacuo gave an orange foam 3-[2-(aminomethyl)-6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)phenyl]-1-propanol (2.73 g, 3.95 mmol, 18.9 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (inter alia) 8.23 (1H, d), 8.05 (1H, dd), 7.86 (1H, d), 7.46 (1H, d), 7.34 (1H, t), 7.06 (1H, d), 4.72 (1H, sept), 4.03 (2H, s), 3.47 (2H, t), 3.27 (2H, t), 1.78 (2H, quin), 1.45 (6H, d); MS (ES) $C_{21}H_{24}{}^{35}ClN_3O_3$ requires 401; found 402 $[M+H]^+$.

Preparation 24

1,1-Dimethylethyl [6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2*H*-2-benzazepin-2-yl]acetate



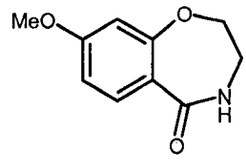
To a solution of 3-[2-(aminomethyl)-6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)phenyl]-1-propanol (Preparation 23) (424 mg, 1.055 mmol) and triphenylphosphine (1384 mg, 5.28 mmol) in dry DCM (150 ml) at RT under Ar was added DIAD (0.974 ml, 5.01 mmol) dropwise over 2 min and the resulting pale yellow solution stirred at RT for 2 hrs. The solution was concentrated to ~10 ml, then passed down an SCX-2 cartridge (10 g), washing with MeOH. The product was

eluted with 0.5M NH_3 in MeOH; concentration in vacuo gave a pale orange oil (>900 mg). SCX-2 purification was repeated to remove remaining triphenylphosphine oxide to give a pale yellow oil (314 mg). The oil was redissolved in DCM (40 ml), BOC_2O (0.367 ml, 1.583 mmol) and DMAP (6.44 mg, 0.053 mmol) added sequentially and stirred under Ar for 2 hrs. Saturated aqueous NH_4Cl (20 ml) was added then the aqueous extracted with DCM (25 ml). The organic layers were combined, passed through a hydrophobic frit and concentrated in vacuo to give a crude pale brown oil (496 mg). Flash chromatography (silica; Flash 25M; linear gradient (0.1-1%) MeOH in DCM) gave a yellow oil 1,1-dimethylethyl 6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepine-2-carboxylate (130 mg). This material was redissolved in 4 M HCl in dioxane (5 ml, 20.00 mmol) and stirred at RT for 3 hrs. The solution was added to an SCX-3 column (10 g) and washed with MeOH. The product was eluted with 0.5 M NH_3 in MeOH; concentration in vacuo gave a pale white solid (102 mg).The product was redissolved in dry DMF (3 ml); potassium carbonate (74.1 mg, 0.536 mmol) and tert-butyl bromoacetate (0.042 ml, 0.281 mmol) were added, then the suspension irradiated to 100 °C for 10 min in the microwave. The mixture was diluted with DCM (7 ml), then added to an SCX-3 cartridge (10 g) and washed with MeOH. The product was eluted with 0.5 M NH_3 in MeOH; concentration in vacuo gave an orange oil (57 mg). Reverse-phase mass-directed auto-purification (MDAP) gave the product in a water-MeCN solution. The desired fractions were added to an SCX-3 cartridge (1g) and washed with MeOH. The product was eluted with 0.5 M NH_3 in MeOH; concentration in vacuo gave a clear film (21.4 mg) a 5:2 ratio mixture of 1,1-dimethylethyl [6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]acetate and [6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]acetic acid. Major component: ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (1H, d), 8.05 (1H, dd), 7.68 (1H, d), 7.26 (1H, d), 7.25 (1H, t), 7.06 (1H, d), 4.72 (1H, sept), 4.14 (2H, s), 3.28 (2H, br s), 3.23 (2H, t), 3.16 (2H, s), 1.77 (2H, m), 1.47 (9H, s), 1.43 (6H, d); MS (ES) $C_{27}H_{32}{}^{35}ClN_3O_4$ requires 497; found 498 $[M+H]^+$.

Preparation 25

8-(Methyloxy)-3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one

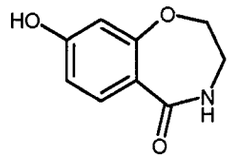
66



DIAD (32.1 ml, 165 mmol) was added dropwise over 15 mins to a stirred, ice-cooled solution of methyl 2-hydroxy-4-(methyloxy)benzoate (24.18 g, 150 mmol), 1,1-dimethylethyl (2-hydroxyethyl)carbamate (27.3 g, 150 mmol) and triphenylphosphine (43.3 g, 165 mmol) in THF (450 ml) then stirred and allowed to warm to room temperature over 2 hours. The reaction mixture was evaporated to give 129.9g of a viscous yellow oil. Trifluoroacetic acid (60 ml, 779 mmol) in dichloromethane (DCM) (350 ml) were added and the reaction left at room temperature for 65 hours then evaporated to dryness. The resultant residue was dissolved in 500ml of ether and extracted with 2M HCl (200ml and 2x75ml). Combined acid extracts were washed with 200ml of ether then 500g of ice added along with 250ml of EtOAc and the mixture basified with 50% sodium hydroxide with vigorous stirring. The organics were separated and the aqueous further extracted with 4x75ml of EtOAc and the combined organics dried (magnesium sulphate) and evaporated to give 21.1g of a yellow oil. The oil was dissolved in toluene (350 ml) and stirred and refluxed for 24 hours then evaporated and purified by flash chromatography eluting with EtOAc to give the title compound (8.61g) as a white solid. MS (ES) $C_{10}H_{11}NO_3$ requires 193; found 194 $[M+H]^+$.

Preparation 26

8-Hydroxy-3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one

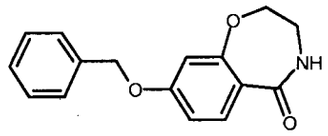


A mixture of 8-(methyloxy)-3,4-dihydro-1,4-benzoxazepin-5(2H)-one (Preparation 25) (7.98 g, 41.3 mmol) and hydrobromic acid (100 ml, 1842 mmol) was stirred and heated at 110 °C for 7 hours. Then the reaction mixture was evaporated and azeotroped twice with 150ml of ethanol to give the title compound (8.66g) light brown solid which was used without purification. MS (ES) $C_9H_9NO_3$ requires 179; found 180 $[M+H]^+$.

Preparation 27

67

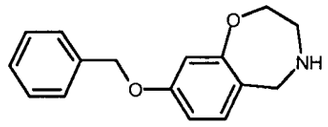
8-[(Phenylmethyl)oxy]-3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one



A mixture of 8-hydroxy-3,4-dihydro-1,4-benzoxazepin-5(2H)-one (Preparation 26) (8.66 g, 48.3 mmol), benzyl bromide (6.32 ml, 53.2 mmol) and potassium carbonate (20.04 g, 145 mmol) in DMF (80 ml) was stirred and heated at 60 °C for 2 hours. The cooled reaction was diluted with EtOAc/water (300 ml of each) and the aqueous extracted with EtOAc (2x75ml). Combined organics were washed with 3x100ml of water, dried (magnesium sulphate), evaporated, triturated with ether and filtered off to give the title compound (8.39g) as a white solid. MS (ES) $C_{16}H_{15}NO_3$ requires 269; found 270 $[M+H]^+$.

Preparation 28

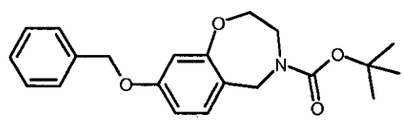
8-[(Phenylmethyl)oxy]-2,3,4,5-tetrahydro-1,4-benzoxazepine



1M Lithium aluminium hydride (62.4 ml, 62.4 mmol) in THF was added under argon to a stirred solution of 8-[(phenylmethyl)oxy]-3,4-dihydro-1,4-benzoxazepin-5(2H)-one (Preparation 27) (8.39 g, 31.2 mmol) in THF (150 ml) with ice bath cooling over 5 minutes. The resulting solution was heated with stirring at 60 °C for 3 hours. The reaction was cooled and carefully quenched by slow addition with ice cooling of 150ml of 2M sodium hydroxide followed by 150ml of EtOAc. The organics were separated and aqueous extracted with 100ml of EtOAc. The combined organic extracts were dried (magnesium sulphate) and evaporated to give the title compound (7.53g) as a light coloured oil. MS (ES) $C_{16}H_{17}NO_2$ requires 255; found 256 $[M+H]^+$.

Preparation 29

1,1-Dimethylethyl 8-[(phenylmethyl)oxy]-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate

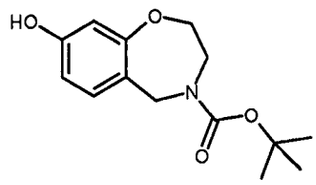


68

BOC_2O (7.52 ml, 32.4 mmol) was added to a solution of 8-[(phenylmethyl)oxy]-2,3,4,5-tetrahydro-1,4-benzoxazepine (Preparation 28) (7.52 g, 29.5 mmol) in DCM (100 ml) and kept at room temperature for 30 minutes. Then the reaction was evaporated to dryness and purified by flash chromatography eluting with 5% EtOAc in iso-hexane changing to 15% EtOAc in iso-hexane to elute product. Triturated with iso-hexane and filtered off to give 7.37g of white solid. MS (ES) $C_{21}H_{25}NO_4$ requires 355; found 300 $[M+H-56]^+$.

Preparation 30

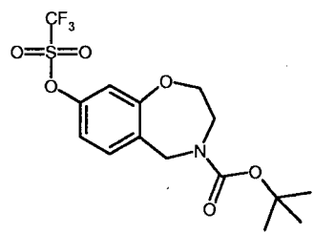
1,1-Dimethylethyl 8-hydroxy-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate



1,1-Dimethylethyl 8-[(phenylmethyl)oxy]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (Preparation 29) (7.35 g, 20.68 mmol) in a mixture of THF (40 ml) and EtOH (40 ml) was hydrogenated with 10% palladium on carbon (0.735 g, 6.91 mmol) for 18 hours then filtered and evaporated to give the title compound (5.49g) as a white solid. MS (ES) $C_{14}H_{19}NO_4$ requires 265; found 166 $[M+H-100]^+$.

Preparation 31

1,1-Dimethylethyl 8-{[(trifluoromethyl)sulfonyl]oxy}-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate

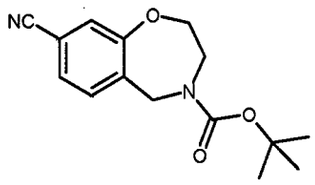


Trifluoromethanesulfonic anhydride (0.253 ml, 1.498 mmol) was added to an ice cooled solution of 1,1-dimethylethyl 8-hydroxy-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (Preparation 30) (0.265 g, 0.999 mmol) in pyridine (4 ml) and stirred for one hour. The reaction mixture was evaporated, dissolved in 40ml of EtOAc and washed with 20ml of 2M HCl and 20ml of saturated sodium bicarbonate then dried (magnesium sulphate) and evaporated to give the title compound (399mgs) as a yellow gum. MS (ES) $C_{15}H_{18}F_3NO_6S$ requires 397; found 298 $[M+H-100]^+$.

69

Preparation 32

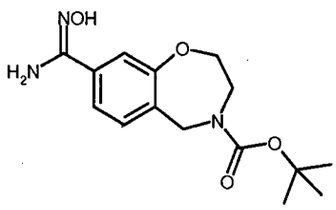
1,1-Dimethylethyl 8-cyano-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate



A mixture of 1,1-dimethylethyl 8-{[(trifluoromethyl)sulfonyl]oxy}-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (Preparation 31) (0.397 g, 0.999 mmol), zinc cyanide (0.176 g, 1.499 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.115 g, 0.100 mmol) in DMF (4 ml) was stirred and heated at 80 °C for 2 hours then cooled and diluted with EtOAc/water (40ml of each) and the organic washed with 3x20ml of water, dried (magnesium sulphate), evaporated and purified by flash chromatography eluting with 1:4 EtOAc/iso-hexane to give the title compound (198mgs) as a gum which crystallised slowly. MS (ES) $C_{15}H_{18}N_2O_3$ requires 274; found 175 $[M+H-100]^+$.

Preparation 33

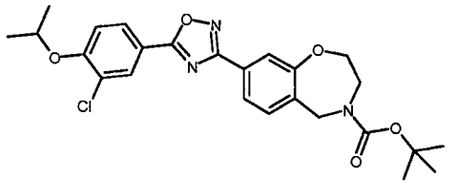
1,1-Dimethylethyl 8-[(hydroxyamino)(imino)methyl]-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate



A mixture of 1,1-dimethylethyl 8-cyano-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (Preparation 32) (0.195 g, 0.711 mmol), hydroxylamine hydrochloride (0.099 g, 1.422 mmol) and sodium bicarbonate (0.299 g, 3.55 mmol) in ethanol (5 ml) was stirred and heated at 60 °C for 3 hours. The reaction mixture was cooled, evaporated and dissolved in EtOAc/water (40ml of each, some warming needed) and the organics dried (magnesium sulphate) and evaporated to give the title compound (210mgs) as a white solid. MS (ES) $C_{15}H_{21}N_3O_4$ requires 307; found 308 $[M+H]^+$.

Preparation 34

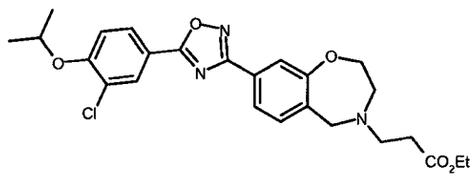
1,1-Dimethylethyl 8-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate



A mixture of 1,1-dimethylethyl 8-[(hydroxyamino)(imino)methyl]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (Preparation 33) (0.195 g, 0.634 mmol), 3-chloro-4-[(1-methylethyl)oxy]benzoic acid (Preparation 6) (0.136 g, 0.634 mmol), EDC (0.146 g, 0.761 mmol) and HOBT (0.107 g, 0.698 mmol) DMF (4 ml) was stirred at room temperature for 20 minutes then heated at 100 °C for 17 hours. The cooled reaction mixture was diluted with EtOAc/water (40ml of each) and the organics collected, dried (magnesium sulphate), evaporated and purified by biotage chromatography in 1:4 EtOAc/iso-hexane to give the title compound (172mgs) as a white solid. MS (ES) $C_{25}H_{28}{}^{35}ClN_3O_5$ requires 485; found 486 $[M+H]^+$; $C_{25}H_{28}{}^{37}ClN_3O_5$ requires 487; found 488 $[M+H]^+$.

Preparation 35

Ethyl 3-[8-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]propanoate

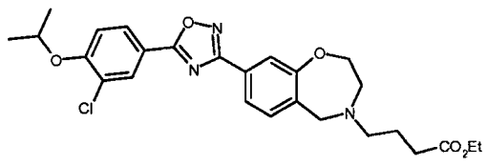


A mixture of 8-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine (Example 13) (0.036 g, 0.199 mmol), ethyl 3-bromopropanoate (0.084 g, 0.199 mmol) and DIPEA (0.097 ml, 0.557 mmol) was stirred and heated at 80 °C for 4 hours when a further portion of ethyl 3-bromopropanoate (0.084 g, 0.199 mmol) and DIPEA (0.097 ml, 0.557 mmol) were added and heated overnight when a further portion of ethyl 3-bromopropanoate (0.084 g, 0.199 mmol) and DIPEA (0.097 ml, 0.557 mmol) were added and heated for 3 more hours when all starting material gone. The cooled reaction mixture was diluted with EtOAc/water (30ml of each) and the organics dried (magnesium sulphate), evaporated and purified by flash chromatography eluting with 1:1

EtOAc/iso-hexane to give the title compound (90mgs) as a colourless gum. MS (ES) $C_{25}H_{28}{}^{35}ClN_3O_5$ requires 485; found 486 $[M+H]^+$.

Preparation 36

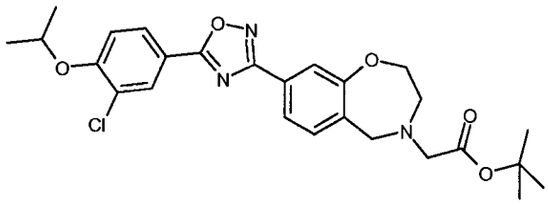
Ethyl 4-[8-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]butanoate



A mixture of 8-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine (Example 13) (0.127 g, 0.3 mmol), DIPEA (0.052 ml, 0.300 mmol) and ethyl 4-bromobutanoate (0.059 g, 0.300 mmol) in acetonitrile (5 ml) was stirred and heated at 70 °C for 15 hours. The cooled reaction mixture was diluted and dissolved in EtOAc/water (30ml of each) and the organics dried (magnesium sulphate), evaporated and purified by flash chromatography eluting with 1:1 EtOAc/iso-hexane to give the title compound (106mgs) as a colourless gum. MS (ES) $C_{26}H_{30}{}^{35}ClN_3O_5$ requires 499; found 500 $[M+H]^+$.

Preparation 37

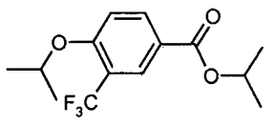
1,1-Dimethylethyl [8-(5-{3-chloro-4-[(1-methylethyl)oxy] phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]acetate



A mixture of 8-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine (Example 13) (0.127 g, 0.301 mmol), 1,1-dimethylethyl bromoacetate (0.117 g, 0.601 mmol) and DIPEA (0.210 ml, 1.203 mmol) in acetonitrile (5 ml) was stirred and heated at 70 °C for one hour. The cooled reaction mixture was diluted with EtOAc/water (30ml of each) and the organics dried (magnesium sulphate), evaporated and purified by flash chromatography eluting with 1:2 EtOAc/iso-hexane to give the title compound (130mgs) as a colourless gum. MS (ES) $C_{26}H_{30}{}^{35}ClN_3O_5$ requires 499; found 500 $[M+H]^+$.

Preparation 38

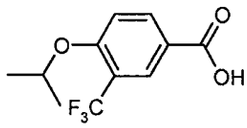
1-Methylethyl 4-[(1-methylethyl)oxy]-3-(trifluoromethyl) benzoate



A mixture of 4-hydroxy-3-(trifluoromethyl)benzoic acid (2.5 g, 12.1 mmol), 2-iodopropane (2.42 ml, 24.3 mmol) and potassium carbonate (3.35 g, 24.3 mmol) in N,N'-dimethylformamide (200 ml) was heated at 70 °C for 4 hrs. The reaction mixture was partially concentrated in vacuo and the residue partitioned between EtOAc (150 ml) and water (150 ml) containing some aqueous sodium hydroxide. The aqueous phase was extracted with further EtOAc (2 x 100 ml) and the combined organic fractions dried (hydrophobic frit phase separator) and concentrated in vacuo to give the crude title compound as a yellow oil (3.6 g, 12.1 mmol). δH (d_6DMSO, 400 MHz): 8.16 (1H, dd), 8.08 (1H, d), 7.43 (1H, d), 5.13 (1H, septet), 4.91 (1H, septet), 1.32 (12H, d).

Preparation 39

4-[(1-Methylethyl)oxy]-3-(trifluoromethyl)benzoic acid

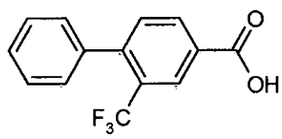


To a mixture of 1-methylethyl 4-[(1-methylethyl)oxy]-3-(trifluoromethyl)benzoate (Preparation 38) (3.63 g, 12.5 mmol) in ethanol (100 ml) was added aqueous sodium hydroxide (12.5 M, 10.0 ml, 125 mmol) and the reaction heated to reflux for 3 hrs. The mixture was concentrated in vacuo and the residue partitioned between EtOAc (100 ml) and water (100 ml) and acidified with aqueous hydrochloric acid. The aqueous layer was extracted further with EtOAc (100 ml) and the combined organic layers dried and concentrated in vacuo to give the title compound as a yellow solid (2.68 g, 10.8 mmol). MS (ES-): $C_{11}H_{11}F_3O_3$ requires 248; found 247 [M-H$^+$].

Preparation 40

2-(Trifluoromethyl)-4-biphenylcarboxylic acid

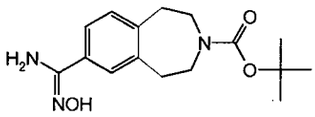
F3



The reaction was split into 4, using a quarter of the reagents shown in each: to a mixture of 4-bromo-3-(trifluoromethyl)benzonitrile (4 g, 16.00 mmol), phenylboronic acid (3.90 g, 32.0 mmol) and potassium carbonate (6.63 g, 48.0 mmol) in DMF (64 ml) was added palladium tetrakistriphenylphosphine(0) (1.849 g, 1.600 mmol). Each reaction was heated in the microwave at 150 °C for 30 minutes. The combined reaction mixtures were filtered through Celite®, washed with EtOAc and the solvent removed in vacuo. The residue was partitioned between EtOAc (100 ml) and water (100 ml) and the organic phase washed with sodium bicarbonate solution (100 ml). The organic phase was dried ($MgSO_4$), filtered and the solvent removed in vacuo. The brown oil was triturated with DCM and filtered to give a pale yellow solid, 2-(trifluoromethyl)-4-biphenylcarboxamide (2.47 g) which was used without further purification. To 2-(trifluoromethyl)-4-biphenylcarboxamide (2 g, 7.54 mmol) in ethanol (80 ml) was added potassium hydroxide (4.23 g, 75 mmol) and water and the mixture heated to 90 °C for 18 hrs. The reaction mixture was concentrated in vacuo and the residue partitioned between DCM (100 ml) and 2M HCl (100 ml). The organic phase was isolated and dried (hydrophobic frit phase separator) and the solvent removed in vacuo to give the crude product. Chromatographic purification using the Biotage Horizon, reverse phase cartridge, eluting 5-100 % MeCN in water to give the title compound as an off-white solid (960 mg). LCMS (ES-): $C_{14}H_9F_3O_2$ requires 266; found 265 [M-H$^+$]

Preparation 41

1,1-Dimethylethyl 7-[(hydroxyamino)(imino)methyl]-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate

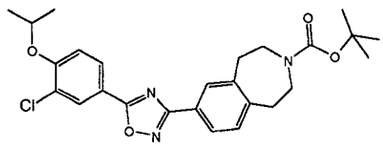


A suspension of 1,1-dimethylethyl 7-cyano-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (may be prepared as described in WO2002040471) (5 g, 18.36 mmol), hydroxylamine hydrochloride (2.55 g, 36.7 mmol) and sodium bicarbonate (7.71 g, 92 mmol) in ethanol (250 ml) was heated at 50°C overnight. Further hydroxylamine hydrochloride (0.638 g, 9.18 mmol) was added to the reaction mixture and heating at 50°C continued for 5h. The reaction mixture was allowed to cool and the solid filtered

off, the solution was concentrated in vacuo to yield the title compound as a white solid (5.77 g, 17.01 mmol, 93 % yield). δH (d_6DMSO, 400 MHz): 9.56 (1H, s), 7.52-7.37 (2H, m), 7.14 (1H, d), 5.77 (2H, br s), 3.50-3.32 (4H, m), 2.91-2.80 (4H, m), 1.41 (9H, s). MS (ES): $C_{16}H_{23}N_3O_3$ requires 305; found 306 $[M+H]^+$.

Preparation 42

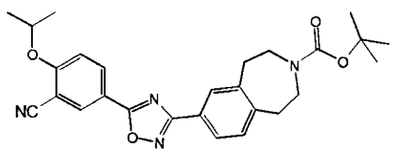
1,1-Dimethylethyl 7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate



To a solution of 3-chloro-4-[(1-methylethyl)oxy]benzoic acid (Preparation 6) (1.406 g, 6.55 mmol) in DMF was added HOBT (1.103 g, 7.20 mmol) and EDC (1.381 g, 7.20 mmol), the resultant solution was stirred under argon for 10 mins at room temp. 1,1-dimethylethyl 7-[(hydroxyamino)(imino)methyl]-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (Preparation 41)(2 g, 6.55 mmol) was then added to the reaction mixture and the solution heated at 80°C overnight. The solvent was removed in vacuo and the residue dissolved in methanol for purification by Biotage Horizon, reverse phase cartridge, eluting 5-100 % acetonitrile in water. The product containing fractions (last 5) were concentrated in vacuo to yield the title compound as a yellow oil (950 mg, 1.87 mmol, 29 % yield). δH (d_6DMSO, 400 MHz): 8.19 (1H, d), 8.11 (1H, dd), 7.83-7.89 (2H, m), 7.45 (1H, d), 7.37 (1H, d), 4.89 (1H, sept), 3.50 (4H, br.s), 2.96 (4H, br.s), 1.41 (9H, s), 1.36 (6H, d). MS (ES): $C_{26}H_{30}{}^{35}ClN_3O_4$ requires 483; found 384 $[M+H-100]^+$.

Preparation 43

1,1-Dimethylethyl-7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate

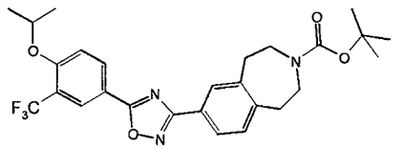


3-Cyano-4-[(1-methylethyl)oxy]benzoic acid (can be prepared as described in WO2005/58848) (687 mg, 3.63 mmol), HOBT (539 mg, 3.99 mmol) and EDC (762 mg, 3.99 mmol) were stirred in DMF (30 ml) under argon for 20 minutes. 1,1-dimethylethyl 7-[(hydroxyamino)(imino)methyl]-1,2,4,5-tetrahydro-3H-3-benzazepine-

3-carboxylate (Preparation 41) (1.11 g, 3.63 mmol) was added and the mixture stirred at room temperature for 4 h before it was heated to 80 °C for 20 h. The reaction mixture was partitioned between EtOAc (80 ml) and water (80 ml) and the organic layer washed with aqueous sodium bicarbonate and water before it was dried in the usual manner and evaporated. The residue was triturated with methanol to give the title compound as a white solid (981 mg, 2.07 mmol). δH (d_6DMSO, 400 MHz): 8.50 (1H, d), 8.40 (1H, dd), 7.88 (1H, br.s), 7.85 (1H, dd), 7.56 (1H, d), 7.38 (1H, d), 4.98 (1H, septet), 3.53-3.47 (4H, m), 3.00-2.92 (4H, m), 1.41 (9H, s), 1.39 (6H, d).

Preparation 44

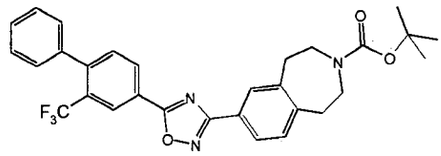
1,1-Dimethylethyl 7-{5-[4-[(1-methylethyl)oxy]-3-(trifluoro-methyl)phenyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate



4-[(1-Methylethyl)oxy]-3-(trifluoromethyl)benzoic acid (Preparation 39) (744 mg, 3.00 mmol), HOBT (446 mg, 3.30 mmol) and EDC (630 mg, 3.30 mmol) were stirred in DMF (28 ml) under argon for 20 minutes. 1,1-dimethylethyl 7-[(hydroxyamino)(imino)methyl]-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (Preparation 41) (915 mg, 3.00 mmol) was added and the mixture stirred at room temperature for 2 hrs before it was heated to 80 °C for 20 hrs. The reaction mixture was partitioned between EtOAc and water and the organic layer washed with aqueous sodium bicarbonate before it was dried in the usual manner and evaporated. The residue was purified by Biotage Horizon, reverse phase cartridge, eluting with 5-100% acetonitrile in water to give the title compound (749 mg, 1.45 mmol). δH (d_6DMSO, 400 MHz): 8.40 (1H, dd), 8.31 (1H, d), 7.89 (1H, br.s), 7.86 (1H, dd), 7.58 (1H, d), 7.37 (1H, d), 4.98 (1H, septet), 3.54-3.46 (4H, m), 3.00-2.92 (4H, m), 1.41 (9H, s), 1.36 (6H, d).

Preparation 45

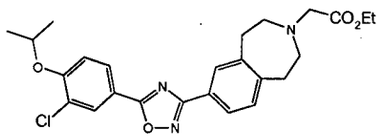
1,1-Dimethylethyl 7-{5-[2-(trifluoromethyl)-4-biphenylyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate



2-(Trifluoromethyl)-4-biphenylcarboxylic acid (Preparation 40) (284 mg, 1.07 mmol), HOBT (159 mg, 1.18 mmol) and EDC (225 mg, 1.18 mmol) were stirred in DMF (10 ml) under argon for 20 minutes. 1,1-Dimethylethyl 7-[(hydroxyamino)(imino)methyl]-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (Preparation 41) (326 mg, 1.07 mmol) was added and the mixture stirred at room temperature for 2.5 h before it was heated to 80 °C for 16 h. The reaction mixture was partitioned between EtOAc (30 ml) and water (30 ml) and the organic layer washed with aqueous sodium bicarbonate and water before it was dried (phase separator) and evaporated. The residue was triturated with methanol to give the title compound as a white solid (370 mg, 0.69 mmol). The filtrate was purified by Biotage Horizon, reverse phase cartridge, eluting with 5-100% acetonitrile in water to give further title compound (70 mg, 0.13 mmol). δH (d_6DMSO, 400 MHz): 8.52 (1H, s), 8.50 (1H, d), 7.93 (1H, s), 7.90 (1H, dd), 7.74 (1H, d) 7.56-7.48 (3H, m), 7.41-7.38 (3H, m), 3.55-3.47 (4H, m), 3.02-2.93 (4H, m), 1.41 (9H, s).

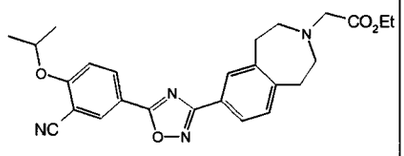
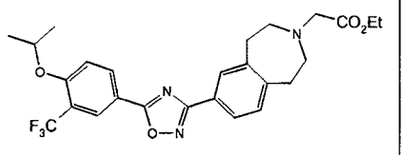
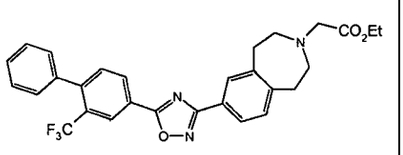
Preparation 46

Ethyl [7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]acetate



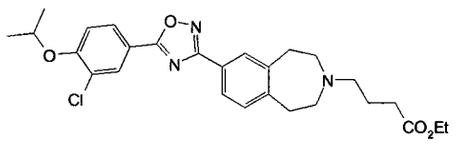
7-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (Example 17) (100 mg, 0.238 mmol), ethyl bromoacetate (0.043 ml, 0.391 mmol) and cesium carbonate (170 mg, 0.521 mmol) were stirred at room temperature in DMF for 5 hours. The reaction mixture was diluted with diethyl ether (~20ml) and washed with water (2x ~20ml), the organic layer was passed through a phase separating cartridge to dry and concentrated in vacuo to yield the title compound (77 mg, 0.16 mmol, 60 % yield) as a yellow oil. δH (d_6DMSO, 400 MHz): 8.19 (1H, s), 8.11 (1H, dd), 7.81-7.85 (2H, m), 7.45 (1H, d), 7.34 (1H, d), 4.89 (1H, sept), 4.07 (2H, q) 3.42 (2H, s), 3.00-291 (4H, m), 2.77-2.72 (4H, m), 1.36 (6H, d), 1.19 (3H, t). MS (ES): $C_{25}H_{28}{}^{35}ClN_3O_4$ requires 469; found 470 $[M+H]^+$.

The following compounds were made by similar methods. Preparation 49 was further purified by MDAP.

Preparation	Structure	Name	m/z
47		ethyl [7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl]acetate	461 $[M+H]^+$
48		ethyl (7-{5-[4-[(1-methylethyl)oxy]-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl)acetate	504 $[M+H]^+$
49		ethyl (7-{5-[2-(trifluoromethyl)-4-biphenylyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl)acetate	522 $[M+H]^+$

Preparation 50

Ethyl 4-[7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl]butanoate

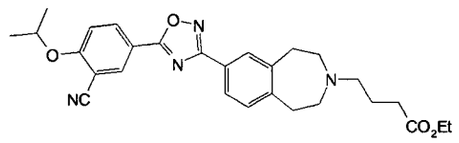


7-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (Example 17) (65 mg, 0.155 mmol), DIPEA (0.104 ml, 0.593 mmol) and ethyl 4-bromobutanoate (0.048 ml, 0.339 mmol) were stirred at 60°C in DMF (10 ml) for 24 hours. The reaction mixture was partitioned between EtOAc (~30ml) and water (~30ml) and the aqueous layer extracted once more with

EtOAc (~40ml). The combined organics were concentrated in vacuo to yield the crude title compound (100 mg, 0.171 mmol) as an orange solid. MS (ES): $C_{27}H_{32}{}^{35}ClN_3O_4$ requires 497; found 498 $[M+H]^+$.

Preparation 51

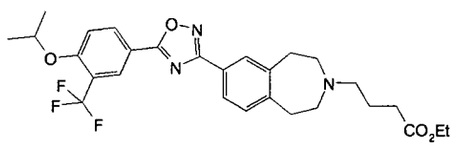
Ethyl 4-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl]butanoate



2-[(1-Methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1,2,4-oxadiazol-5-yl]benzonitrile hydrochloride (Example 18) (200 mg, 0.534 mmol), DIPEA (0.327 ml, 1.869 mmol) and ethyl 4-bromobutanoate (0.153 ml, 1.068 mmol) were stirred at room temperature in DMF (10 ml) for 5 hours, the reaction mixture then heated to 60°C for 5h, the reaction mixture was allowed to stand overnight at room temperature, further ethyl 4-bromobutanoate (0.076 ml, 0.534 mmol) was added and the reaction mixture heated at 60°C for 6 hours. The reaction mixture was partitioned between ethylacetate (~30ml) and water (~30ml) and the aq. layer extracted once more with ethylacetate (~40ml). The combined organics were concentrated in vacuo to yield the title compound (218 mg, 0.402 mmol) as an orange oil. MS (ES): $C_{28}H_{32}N_4O_4$ requires 488; found 489 $[M+H]^+$.

Preparation 52

Ethyl 4-(7-{5-[4-[(1-methylethyl)oxy]-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl)butanoate

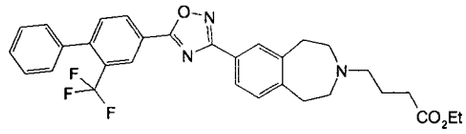


7-{5-[4-[(1-Methylethyl)oxy]-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (Example 19) (160mg, 0.353 mmol), DIPEA (0.234 ml, 1.342 mmol) and ethyl 4-bromobutanoate (0.110 ml, 0.767 mmol) were stirred at room temperature in DMF (10 ml) for 5 hours. The reaction mixture was then heated to 60°C for 5h, and allowed to stand overnight at room temperature. Further ethyl 4-bromobutanoate (0.055 ml, 0.383 mmol) was added and the reaction mixture heated at 60°C for 6 hours. The reaction mixture was partitioned between

EtOAc (~30ml) and water (~30ml) and the aqueous layer extracted once more with EtOAc (~40ml). The combined organics were concentrated in vacuo to yield the title compound (183 mg, 0.310 mmol) as an orange solid. MS (ES): $C_{28}H_{32}F_3N_3O_4$ requires 531; found 532 $[M+H]^+$.

Preparation 53

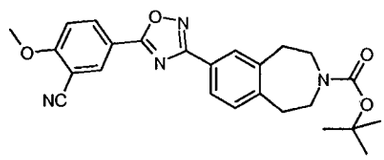
Ethyl 4-(7-{5-[2-(trifluoromethyl)-4-biphenylyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl)butanoate



7-{5-[2-(Trifluoromethyl)-4-biphenylyl]-1,2,4-oxadiazol-3-yl}-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (Example 20) (200 mg, 0.424 mmol), DIPEA (0.281 ml, 1.608 mmol) and ethyl 4-bromobutanoate (0.131 ml, 0.919 mmol) were stirred at RT in DMF (10 ml) for 5 hours. The reaction mixture was then heated to 60°C for 5hrs, and then allowed to stand overnight at room temperature. Further ethyl 4-bromobutanoate (0.066 ml, 0.459 mmol) was added and the reaction mixture heated at 60°C for 6 hours. The reaction mixture was partitioned between EtOAc (~30ml) and water (~30ml) and the aqueous layer extracted once more with EtOAc (~40ml). The combined organics were concentrated in vacuo to yield the title compound (277 mg, 0.454 mmol) as an orange solid. MS (ES): $C_{31}H_{30}F_3N_3O_3$ requires 549; found 550 $[M+H]^+$.

Preparation 54

1,1-Dimethylethyl 7-{5-[3-cyano-4-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate

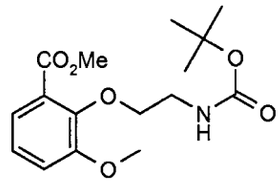


1,1-Dimethylethyl 7-[(hydroxyamino)(imino)methyl]-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (Preparation 41) (240 mg, 0.785 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil) (23.01 mg, 0.575 mmol) in THF (5 ml) at room temperature (note slight effervescence). The resultant mixture was stirred at room temperature for 30mins, methyl 3-cyano-4-(methyloxy)benzoate (100 mg, 0.523 mmol) was then added and the reaction mixture

was heated to reflux (75°C) for 45 mins. The reaction mixture was diluted with water and ethylacetate and the layers partitioned, solid was present in the bi-phasic mixture so this was transferred to a conical flask and stirred at room temperature for 2h at room temperature. The mixture was then partitioned and the organic layer concentrated in vacuo. to yield the title compound (280 mg, 0.502 mmol, 96 % yield) as a yellow oil. MS (ES): $C_{25}H_{26}N_4O_4$ requires 447; no mass ion present. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1H, d (8.44), 1H, dd (8.38), 2H, m (7.89-7.95), 1H, m (7.35-7.42), 1H, m (7.13-7.17), 3H, s (4.06), 4H, m (3.50-3.66), 4H, m (2.87-3.06), 9H, s (1.50).

Preparation 55

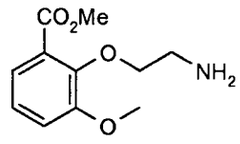
Methyl 2-{[2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)ethyl] oxy}-3-(methyloxy)benzoate



DIAD (23.95 ml, 123 mmol) was added dropwise to a stirred solution of 1,1-dimethylethyl (2-hydroxyethyl)carbamate (18.05 g, 112 mmol), methyl 2-hydroxy-3-(methyloxy)benzoate (20.4 g, 112 mmol) and triphenylphosphine (32.3 g, 123 mmol) in THF (400 ml) with cooling in an ice/water bath. Stirred for 30 mins then evaporated and used without any purification. LC/MS showed essentially just product and triphenylphosphine oxide. Yield 98.9g of crude material. MS (ES): $C_{16}H_{23}NO_6$ requires 325; found 326 $[M+H]^+$.

Preparation 56

Methyl 2-[(2-aminoethyl)oxy]-3-(methyloxy)benzoate

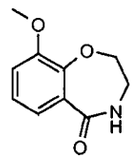


Methyl 2-{[2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)ethyl]oxy}-3-(methyloxy)benzoate (Preparation 55) (98.9 g, 304 mmol) (crude material, in reality only contained a maximum of 0.112 mols or 36.4g) was dissolved in a mixture of TFA (60 ml, 779 mmol) and DCM (60 ml) and left at room temperature for 1.5 hrs. Evaporated and dissolved in EtOAc/2M HCl (250ml of each) and the organic extracted with a further

2x100ml of EtOAc. 250ml of EtOAc added to aqueous and 500g of ice added and solution basified with 50% sodium hydroxide. Organic separated and aqueous extracted with a further 5x75ml of EtOAc. Combined organics dried (magnesium sulphate) and evaporated to give 11.9g of colourless oil. LC/MS showed 13% product and 87% of material already cyclised to the benzoxazepine. MS (ES): $C_{11}H_{15}NO_4$ requires 225; found 226 $[M+H]^+$.

Preparation 57

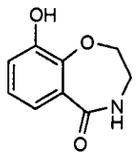
9-(Methyloxy)-3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one



A solution of methyl 2-[(2-aminoethyl)oxy]-3-(methyloxy)benzoate (Preparation 56) (11.9 g, 52.8 mmol) in toluene (200 ml) was stirred and heated at 110°C for 1 hour then cooled and evaporated to give the title compound (10.3g) as a sandy coloured solid. MS (ES): $C_{10}H_{11}NO_3$ requires 193; found 194 $[M+H]^+$.

Preparation 58

9-Hydroxy-3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one

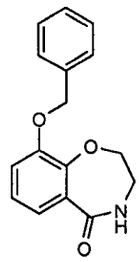


9-(Methyloxy)-3,4-dihydro-1,4-benzoxazepin-5(2H)-one (Preparation 57) (9.3 g, 48.1 mmol) in hydrobromic acid (120 ml, 2210 mmol) was stirred and heated at 105°C for 5 hours. Evaporated to dryness, azeotroped with 200ml of ethanol and biotage chromatographed twice in 3% methanol in EtOAc. Triturated with EtOAc and filtered off to give 6.61g of white solid. MS (ES): $C_9H_9NO_3$ requires 179; found 180 $[M+H]^+$.

Preparation 59

9-[(Phenylmethyl)oxy]-3,4-dihydro-1,4-benzoxazepin-5(2H)-one

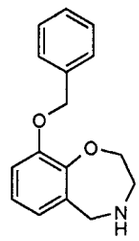
82



A mixture of 9-hydroxy-3,4-dihydro-1,4-benzoxazepin-5(2H)-one (7.46 g, 41.6 mmol), benzyl bromide (Preparation 58) (5.45 ml, 45.8 mmol) and potassium carbonate (17.26 g, 125 mmol) was stirred and heated at 60°C in DMF (75 ml) for 2 hours. Cooled, diluted with water (300ml) and extracted with EtOAc (200ml and 4x75ml) and the combined organics washed with 3x100ml of water. Dried (magnesium sulphate), evaporated, triturated with ether and filtered off to give 7.55g of white solid. MS (ES): $C_{16}H_{15}NO_3$ requires 269; found 270 $[M+H]^+$.

Preparation 60

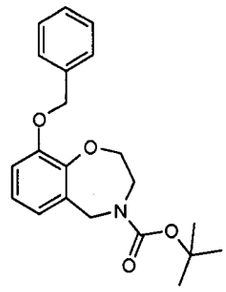
9-[(Phenylmethyl)oxy]-2,3,4,5-tetrahydro-1,4-benzoxazepine



1M Lithium aluminum hydride (60 ml, 60.0 mmol) in THF was added to a stirred solution of 9-[(phenylmethyl)oxy]-3,4-dihydro-1,4-benzoxazepin-5(2H)-one (Preparation 59) (7.4 g, 27.5 mmol) in THF (150 ml) under argon and heated at 60°C for 2 hours then cooled and quenched by careful addition of 100ml of 2M sodium hydroxide with ice bath cooling and the resulting suspension filtered, the solids washed with water and EtOAc and the organic dried (magnesium sulphate) and evaporated to give 7.01g of white solid. MS (ES): $C_{16}H_{17}NO_2$ requires 255; found 256 $[M+H]^+$.

Preparation 61

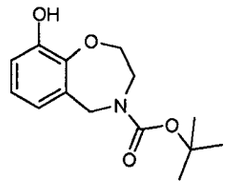
1,1-Dimethylethyl 9-[(phenylmethyl)oxy]-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate



9-[(Phenylmethyl)oxy]-2,3,4,5-tetrahydro-1,4-benzoxazepine (Preparation 60) (7.01 g, 27.5 mmol) and BOC_2O (7.01 ml, 30.2 mmol) were dissolved in DCM (100 ml) and left at room temperature for one hour then evaporated and biotage chromatographed in 5% EtOAc in hexane to remove excess BOC_2O and changing to 15% EtOAc in iso-hexane to elute the title compound (8.25g) as a white solid. MS (ES): $C_{21}H_{25}NO_4$ requires 355; found 256 $[M+H-100]^+$.

Preparation 62

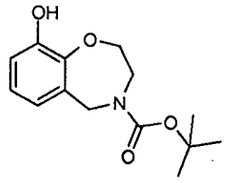
1,1-Dimethylethyl 9-hydroxy-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate



A solution of 1,1-dimethylethyl 9-[(phenylmethyl)oxy]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (Preparation 61) (8.25 g, 23.21 mmol) in ethanol (100 ml) was hydrogenated with 10% palladium on carbon (0.825 g, 7.75 mmol) for 18 hours, filtered and evaporated to give 6.16g of white solid. MS (ES-): $C_{21}H_{25}NO_4$ requires 265; found 264 $[M-H^+]$.

Preparation 62 (Alternative preparation)

1,1-Dimethylethyl 9-hydroxy-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate



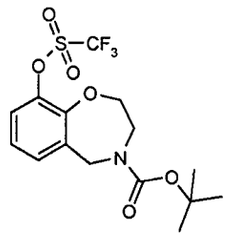
A suspension of 2,3,4,5-tetrahydro-1,4-benzoxazepin-9-ol. hydrobromide (Preparation 85) (55.7 g, 226 mmol) in dichloromethane (DCM) (550 ml) was treated with triethylamine (47.3 ml, 339 mmol) and stirred for 20 minutes. This mixture was

cooled in ice/water to ca 5°C and treated slowly with a solution of BOC_2O (59.6 ml, 249 mmol) in dichloromethane (DCM) (200 ml) at such a rate as to keep the internal temperature below 10°C. When the addition was complete, the mixture was allowed to warm to room temperature, stirred for 2 hours and allowed to stand at room temperature overnight. The mixture was washed with 0.5M hydrochloric acid (2x 250 ml) and water (250 ml), dried (sodium sulphate) and evaporated to give the title compound as a pale brown solid (60.5g)

MS (ES-): $C_{21}H_{25}NO_4$ requires 265; found 264 $[M-H]^+$.

Preparation 63

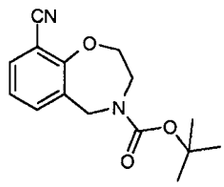
1,1-Dimethylethyl 9-{[(trifluoromethyl)sulfonyl]oxy}-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate



Trifluoromethanesulfonic anhydride (6.04 ml, 35.7 mmol) was added to an ice cooled solution of 1,1-dimethylethyl 9-hydroxy-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (Preparation 62) (6.32 g, 23.82 mmol) in pyridine (100 ml) and stirred at 0°C for 2 hrs. The pyridine was evaporated and the residue dissolved in EtOAc. Washed with 2M HCl, sat sodium bicarbonate solution, dried over magnesium sulphate and evaporated to give the title compound (9g) as a yellow oil. MS (ES): $C_{15}H_{18}F_3NO_6S$ requires 397; found 298 $[M+H-100]^+$.

Preparation 64

1,1-Dimethylethyl 9-cyano-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate

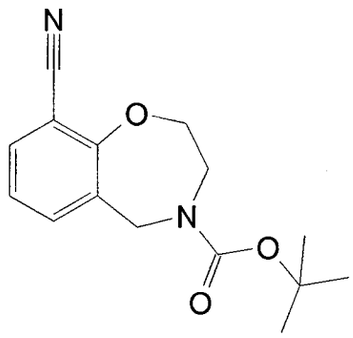


A solution of 1,1-dimethylethyl 9-{[(trifluoromethyl)sulfonyl]oxy}-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (Preparation 63) (9g, 22.65 mmol), zinc cyanide (3.99 g, 34.0 mmol) and tetrakis(triphenylphosphine)palladium(0) (2.62 g, 2.265 mmol) in DMF (90 ml) was heated at 80°C for 24hrs. The reaction was cooled,

diluted with EtOAc (400ml) and water (400ml) and filtered to remove insoluble material. The filtrate was separated and the organic layer washed with water, dried over magnesium sulphate and evaporated. Purified by flash chromatography eluting with EtOAc/iso-hexane 1:9 then 1:3 to give the title compound (5.1g) as a colourless oil. MS (ES): $C_{15}H_{18}N_2O_3$ requires 274; found 174 $[M+H-100]^+$.

Preparation 64 (Alternative preparation)

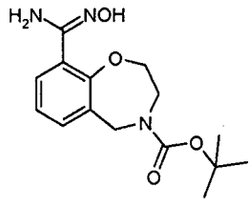
1,1-Dimethylethyl 9-cyano-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate



A solution of 1,1-dimethylethyl 9-bromo-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate (Preparation 101) (1.34 g, 4.08 mmol) in *N,N*-dimethylformamide (11 ml) was degassed under vacuum (3 mm Hg) for 15 min then stirred under nitrogen. Zinc cyanide (575 mg, 4.90 mmol) then tetrakis(triphenylphosphine) palladium(0) (472 mg, 0.41 mmol) were added and the resulting mixture was stirred at 100°C under nitrogen overnight then diluted with ethyl acetate. The insoluble residues were filtered off and washed with ethyl acetate, bleached for two days washed twice with brine, dried over magnesium sulphate and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel, eluting with 15-45% ethyl acetate in cyclohexane gave the title compound as a colourless solid (980 mg). MS (ES) $C_{15}H_{18}N_2O_3$ requires 274 found 275 $[M+H]^+$.

Preparation 65

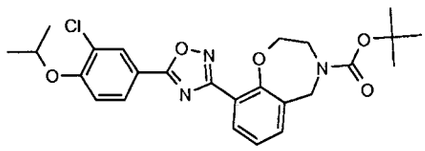
1,1-Dimethylethyl 9-[(hydroxyamino)(imino)methyl]-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate



A suspension of 1,1-dimethylethyl 9-cyano-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (Preparation 64) (5.1g, 18.59 mmol), hydroxylamine hydrochloride (2.58 g, 37.2 mmol) and sodium bicarbonate (7.81 g, 93 mmol) in ethanol (50 ml) was heated at 60°C overnight. A further portion of hydroxylamine hydrochloride (1g) was added and the reaction was heated at 60°C overnight. The solid was filtered from the reaction mixture and the filtrate evaporated. The residue from the evaporation was dissolved in EtOAc, washed with water, dried over magnesium sulphate and evaporated. Trituration with ether to gave the title compound (3.94g) as a white solid. MS (ES): $C_{15}H_{21}N_3O_4$ requires 307; found 308 $[M+H]^+$.

Preparation 66

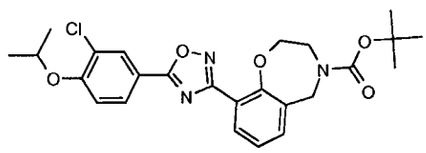
1,1-Dimethylethyl 9-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate



A solution of 1,1-dimethylethyl 9-[(hydroxyamino)(imino)methyl]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (Preparation 65) (500mg, 1.627 mmol), 3-chloro-4-[(1-methylethyl)oxy]benzoic acid (384 mg, 1.790 mmol), EDC (468 mg, 2.440 mmol) and HOBT (299 mg, 1.952 mmol) in DMF (5ml) was stirred at RT overnight then heated at 120°C for 3hrs. The reaction mixture was cooled, diluted with EtOAc/water and the organics dried over magnesium sulfate and evaporated. Purified by flash chromatography eluting with EtOAc/iso-hexane 1:3 to give the title compound (320mg) as a white solid. MS (ES): $C_{25}H_{28}{}^{35}ClN_3O_5$ requires 485; found 486 $[M+H]^+$.

Preparation 66 Alternative Preparation

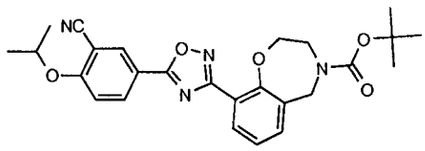
1,1-Dimethylethyl 9-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate



A mixture of 1,1-dimethylethyl 9-[(hydroxyamino)(imino)methyl]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (Preparation 65) (32.9 g, 107 mmol) and triethylamine (17.9 ml, 128 mmol) in dry *N,N*-dimethylformamide (DMF) (200 ml) was cooled in ice/water under nitrogen. A solution of 3-chloro-4-[(1-methylethyl)oxy]benzoyl chloride (Preparation 102) (28.7 g, 123 mmol) in DMF (100 ml) was added over *ca* 20 minutes. When the addition was complete the mixture was allowed to warm to room temperature and stirred for 1 hour at room temperature, then at 120°C for 3 hours. The mixture was allowed to cool and was poured into water (1 litre). The resulting solid was extracted into ethyl acetate (3x 300 ml) and the extracts combined, washed with 1M hydrochloric acid (2x 250 ml), then 1M sodium carbonate solution (3x 250 ml), brine (250 ml), dried (sodium sulphate) and evaporated. The residue was purified by chromatography on silica. Eluting with a 10-40% gradient of ethyl acetate in isohexane to give the title compound as a crystalline solid (42.7g) MS (ES): $C_{25}H_{28}{}^{35}ClN_3O_5$ requires 485; found 486 $[M+H]^+$.

Preparation 67

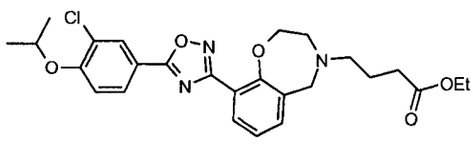
1,1-Dimethylethyl 9-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate



Prepared in a similar way to Preparation 66 from Preparation 65. MS (ES): $C_{26}H_{28}N_4O_5$ requires 476; found 477 $[M+H]^+$.

Preparation 68

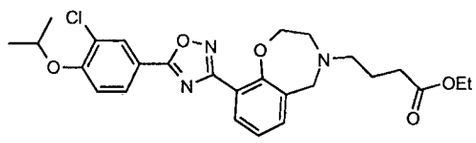
Ethyl 4-[9-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]butanoate



A solution of 9-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrochloride (Example 31) (179 mg, 0.424 mmol), ethyl 4-bromobutanoate (0.061 ml, 0.424 mmol) and DIPEA (0.074 ml, 0.424 mmol) in Acetonitrile (5ml) was heated at 70°C overnight. Additional ethyl 4-bromobutanoate (0.061 ml, 0.424 mmol) and DIPEA (0.074 ml, 0.424 mmol) were added and the reaction heated for a further 5hrs. The cooled reaction was diluted with EtOAc/water, separated, the organics dried over magnesium sulphate and evaporated. Purified by flash chromatoraphy eluting with EtOAc/iso-hexane 1:2 to give the title compound (135mg) as a colourless oil. MS (ES): $C_{26}H_{30}{}^{35}ClN_3O_5$ requires 499; found 500 $[M+H]^+$.

Preparation 68 Alternative Preparation

Ethyl 4-[9-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]butanoate

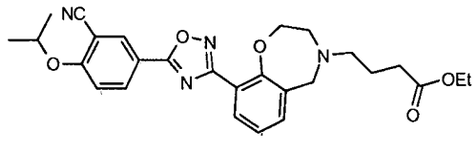


A mixture of 9-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrochloride (Example 31) (20 g, 47.4 mmol), potassium carbonate (16.4 g, 118 mmol) and potassium iodide (7.86 g, 47.4 mmol) in *N,N*-dimethylformamide (DMF) (250 ml) was treated with ethyl 4-bromobutanoate (7.46 ml, 52.1 mmol) and the resulting mixture stirred at 80°C under nitrogen for 180 minutes. The mixture was allowed to cool and poured into water (1000 ml). The resulting precipitate was extracted into ethyl acetate (3x 250 ml) and the extracts combined, washed with water (2x 250 ml), then brine (150 ml), dried (sodium sulphate) and evaporated to give a colourless viscous oil. The crude material was purified by chromatography on silica, eluting with a 20-100% gradient of ethyl acetate in isohexane to give the title compound as a colourless, viscous oil which crystallised on standing (18.3g).

MS (ES): $C_{26}H_{30}{}^{35}ClN_3O_5$ requires 499; found 500 $[M+H]^+$.

Preparation 69

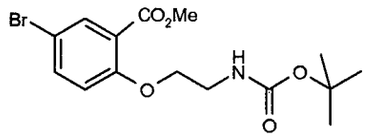
Ethyl 4-[9-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]butanoate



Prepared in a similar way to Preparation 68 from Example 32. MS (ES): $C_{27}H_{30}N_4O_5$ requires 490; found 491 $[M+H]^+$.

Preparation 70

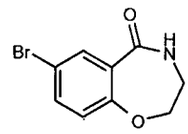
Methyl 5-bromo-2-{[2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)ethyl]oxy}benzoate



DIAD (9.62g, 47.6mmol) was added to a mixture of methyl 5-bromo-2-hydroxybenzoate (10g, 43.3mmol), 1,1-dimethylethyl (2-hydroxyethyl)carbamate (6.98g, 43.3mmol) and triphenylphosphine (12.47g, 47.6mmol) in THF (250ml) and stirred at RT for 2.5hr. Additional triphenylphosphine (2.5g) was added followed by DIAD (4ml) and the mixture left standing overnight. Evaporation and purification by flash chromatography eluting with 25%EtOAc/hexane gave the title compound as a yellow oil (8.92g). MS (ES): $C_{15}H_{20}{}^{81}BrNO_5$ requires 375; found 276 $[M+H-100]^+$.

Preparation 71

7-Bromo-3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one

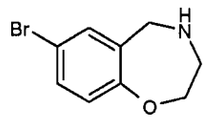


A solution of methyl 5-bromo-2-{[2-({[(1,1-dimethylethyl)oxy]carbonyl}amino)ethyl]oxy}benzoate (Preparation 70) (8.92g, 23.8mmmol) in DCM (18ml) was treated with TFA (7ml) and stirred for 5hrs. Additional (2ml) TFA was added and the reaction left overnight. The solvent was evaporated, re-evaporated with toluene (5x) and dissolved in toluene (50ml). The resulting residue was treated with triethylamine (4 equiv) and heated at 100°C overnight then evaporated. The residue was purified by flash chromatography twice eluting with 50% EtOAc/hexane then 40-45%

EtOAc/hexane. The fractions were evaporated to give the title compound (3.4g) as a white solid. MS (ES): $C_9H_8{}^{81}BrNO_2$ requires 243; found 244 $[M+H]^+$.

Preparation 72

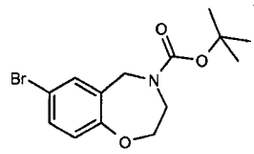
7-Bromo-2,3,4,5-tetrahydro-1,4-benzoxazepine



A solution of 7-bromo-3,4-dihydro-1,4-benzoxazepin-5(2H)-one (Preparation 71) (3.28 g, 13.55 mmol) in tetrahydrofuran (THF) (30ml) was stirred under argon. Borane tetrahydrofuran complex (81 ml, 81 mmol) was added slowly and the solution stirred at RT for 1.5 hrs. The solution was heated at 65°C overnight. The reaction was cooled and MeOH (20ml) added dropwise until fizzing ceased. Then 2M HCl (100ml) was added and the reaction heated at reflux for 1hour before being cooling and solvent removal by evaporation. The reaction mixture was partitioned between EtOAc/Water and separated. The aqueous layer was basified with 2M NaOH, extracted with EtOAc, dried over magnesium sulphate and evaporated to give a colourless oil (1g). Precipitated solid from the initial EtOAc layer was filtered and dried. This solid was dissolved in EtOAc/ 2M NaOH, separated and the organic layer dried over magnesium sulphate and evaporated to give a colourless oil (1.6g). The 2 products were combined to give the title compound (2.6g) as a colourless oil. MS (ES): $C_9H_{10}{}^{81}BrNO$ requires 229; found 230 $[M+H]^+$.

Preparation 73

1,1-Dimethylethyl 7-bromo-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate

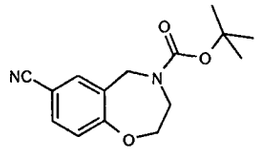


7-Bromo-2,3,4,5-tetrahydro-1,4-benzoxazepine (Preparation 72) (2.15 g, 9.43 mmol) was dissolved in dichloromethane (20 ml). Added triethylamine (1.445 ml, 10.37 mmol) and bis(1,1-dimethylethyl) dicarbonate (2.263 g, 10.37 mmol). Stirred for 4 hours then added dichloromethane and washed with water (3x20ml). Dried the mixture ($MgSO_4$) and evaporated. Separated on biotage column eluting with (EtOAc/Hexane 1:9) and evaporated to give the title compound (2.76g). MS (ES): $C_{14}H_{18}{}^{81}BrNO_3$ requires 329; found 230 $[M+H-100]^+$.

91

Preparation 74

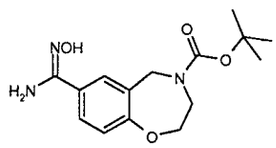
1,1-Dimethylethyl 7-cyano-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate



A mixture of 1,1-dimethylethyl 7-bromo-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (Preparation 73) (2.67g, 8.14 mmol), zinc cyanide (1.715 g, 16.27 mmol) and tetakis(triphenylphosphine)palladium(0) (1.410 g, 1.220 mmol) in DMF (30 ml) was heated at 80°C overnight. Additional tetakis(triphenylphosphine)palladium(0) (700mg) was added and the yellow suspension heated at 80°C for a further 5hrs. The cooled reaction mixture was diluted with EtOAc/water, separated, and organics dried over anhydrous magnesium sulphate and evaporated. The crude was purified by flash chromatography eluting with EtOAc/iso-hexane 1:9. The combined fractions were evaporated to give the title compound (2.01g) as a yellow solid. δH ($CDCl_3$, 400 MHz) : 1.42 (9H, br.s), 3.81 (2H, t), 4.09 (2H, m), 4.43 (1H, s), 4.51 (1H, s), 7.09 (1H, m), 7.47- 7.59 (2H, m).

Preparation 75

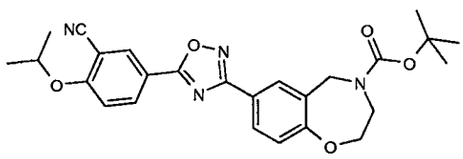
1,1-Dimethylethyl 7-[(hydroxyamino)(imino)methyl]-2,3-dihydro -1,4-benzoxazepine-4(5*H*)-carboxylate



A suspension of 1,1-dimethylethyl 7-cyano-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (Preparation 74) (2.016 g, 7.35 mmol), hydroxylamine hydrochloride (1.021 g, 14.70 mmol) and sodium bicarbonate (3.09 g, 36.7 mmol) in ethanol (30 ml) was heated at 60°C overnight. The grey solid was removed by filtration and the filtrate evaporated. The resulting residue was dissolved in EtOAc, washed with water (3x20ml), dried ($MgSO_4$) and evaporated to give the title compound (1.77g) as a white solid. MS (ES): $C_{15}H_{21}N_3O_4$ requires 307; found 308 $[M+H]^+$.

Preparation 76

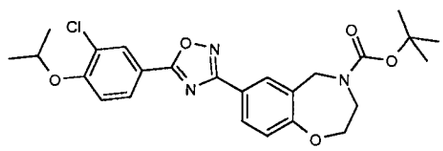
1,1-Dimethylethyl 7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate



A solution of 1,1-dimethylethyl 7-[(hydroxyamino)(imino)methyl]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (Preparation 75) (0.84 g, 2.73 mmol), 3-cyano-4-[(1-methylethyl)oxy]benzoic acid (can be prepared as described in WO2005/58848) (0.617 g, 3.01 mmol), EDC (0.786 g, 4.10 mmol) and HOBT (0.502 g, 3.28 mmol) in DMF (10 ml) was stirred at RT overnight. Additional EDC (0.4g) was added and the reaction stirred for 3 hours. Then additional 3-cyano-4-[(1-methylethyl)oxy]benzoic acid (0.3g) was added, the reaction heated at 120°C for 1hour and left standing overnight. The reaction mixture was partitioned between EtOAc/water, and the organic layer collected, dried ($MgSO_4$) and evaporated. The resulting crude was purified by flash chromatography eluting with EtOAc/iso-hexane 20-30 %. Analysis of the puried fractions by LCMS showed some 3-cyano-4-[(1-methylethyl)oxy]benzoic acid present so sodium bicarbonate and EtOAc was added. The EtOAc layer was separated, dried ($MgSO_4$) and evaporated to give the title compound (410mg) as a white solid. MS (ES): $C_{26}H_{28}N_4O_5$ requires 476; found 421 $[M+H-56]^+$.

Preparation 77

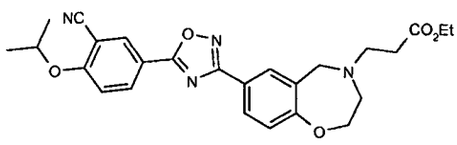
1,1-Dimethylethyl 7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate



The title compound was prepared by a similar method to Preparation 76 using Preparation 75 and the appropriate acid. MS (ES): $C_{25}H_{28}{}^{35}ClN_3O_5$ requires 485; found 430 $[M+H-56]^+$.

Preparation 78

Ethyl 3-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]propanoate

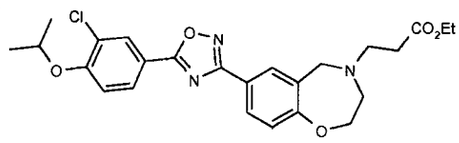


GB

To a solution of 2-[(1-methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1,2,4-oxadiazol-5-yl]benzonitrile hydrochloride (Example 35) (0.101 g, 0.268 mmol) in acetonitrile (2 ml) was added DIPEA (0.094 ml, 0.537 mmol) and ethyl 3-bromopropanoate (0.051 ml, 0.402 mmol). The reaction mixture was stirred and heated at 80°C under Argon for 6 hours. DIPEA (0.094 ml, 0.537 mmol) and ethyl 3-bromopropanoate (0.051 ml, 0.402 mmol) were added and the reaction stirred and heated at 80°C under Argon overnight. Additional quantities of DIPEA (0.094 ml, 0.537 mmol) and ethyl 3-bromopropanoate (0.051 ml, 0.402 mmol) were added and the reaction heated again. The reaction mixture was dissolved in EtOAc, washed with saturated $NaHCO_3$ solution (3x15ml) and water (15ml), dried ($MgSO_4$) and evaporated. The resulting crude was purified by flash chromatography, eluting with EtOAc/iso-Hexane 10-20% (Biotage Column) to give the title compound (92mg). MS (ES): $C_{26}H_{28}N_4O_5$ requires 476; found 477 $[M+H]^+$.

Preparation 79

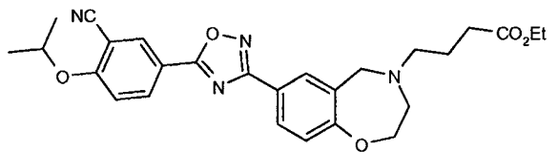
Ethyl 3-[7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]propanoate



Prepared by a similar method to Preparation 78 from Example 36. MS (ES): $C_{25}H_{28}{}^{35}ClN_3O_5$ requires 485; found 486 $[M+H]^+$.

Preparation 80

Ethyl 4-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]butanoate

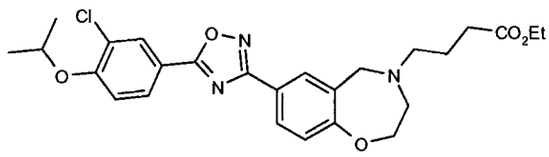


A solution of 2-[(1-methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1,2,4-oxadiazol-5-yl]benzonitrile hydrochloride (Example 35) (0.104 g, 0.276 mmol) was stirred in acetonitrile (2 ml). DIPEA (0.097 ml, 0.553 mmol) and ethyl 4-bromobutanoate (0.059 ml, 0.414 mmol) were added and the reaction mixture stirred and heated at 80°C under Argon for 6 hours. Additional ethyl 4-bromobutanoate (0.059 ml, 0.414 mmol) and DIPEA (0.097 ml, 0.553 mmol) were added and the

reaction mixture stirred and heated at 80°C under argon overnight. Then the reaction mixture was dissolved in EtOAc, washed with saturated $NaHCO_3$ solution (3x15ml) and water (15ml) and the organics dried ($MgSO_4$) and evaporated. The crude was purified by flash chromatography, eluting with EtOAc/iso-Hexane 10-20% (Biotage Column) and evaporated to give the title compound (84mg) as an oil. MS (ES): $C_{27}H_{30}N_4O_5$ requires 490; found 491 $[M+H]^+$.

Preparation 81

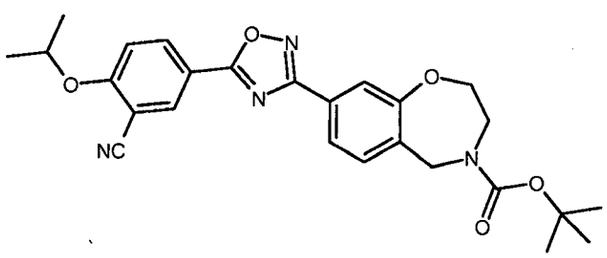
Ethyl 4-[7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]butanoate



7-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine (0.105 g, 0.272 mmol) was stirred in acetonitrile (2 ml). DIPEA (0.095 ml, 0.544 mmol) and ethyl 4-bromobutanoate (0.058 ml, 0.408 mmol) were added and the reaction mixture heated at 80°C under Argon for 5 hours. Additional DIPEA (0.095 ml, 0.544 mmol) and ethyl 4-bromobutanoate (0.058 ml, 0.408 mmol) were added and the reaction mixture heated at 80°C overnight. Then the reaction mixture was dissolved in EtOAc (20ml), washed with $NaHCO_3$ (aq) (15ml x 3) and with water (15ml x 3) and the organics dried ($MgSO_4$) and evaporated. The crude was purified by flash chromatography eluting with EtOAc/iso-Hexane 20/30% (Biotage column), and evaporated to give the title compounds as an oil (80mg). MS (ES): $C_{26}H_{30}{}^{35}ClN_3O_5$ requires 499; found 500 $[M+H]^+$.

Preparation 82

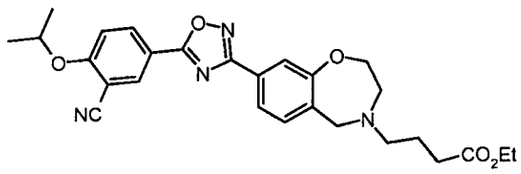
1,1-Dimethylethyl 8-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate



Prepared from Preparation 33 using the appropriate acid using the method described in Preparation 34. MS (ES): $C_{26}H_{28}N_4O_5$ requires 476; found 477 $[M+H]^+$.

Preparation 83

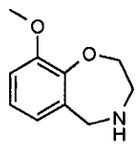
Ethyl 4-[8-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]butanoate



Prepared from Example 41 using the method described in Preparation 36. MS (ES): $C_{27}H_{30}N_4O_5$ requires 490; found 491 $[M+H]^+$.

Preparation 84

9-(Methyloxy)-2,3,4,5-tetrahydro-1,4-benzoxazepine



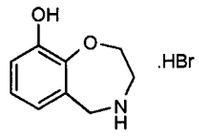
A solution of 9-(methyloxy)-3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one (Preparation 57) (50 g, 259 mmol) in dry tetrahydrofuran (THF) (500 ml) was cooled to *ca* 5°C and treated slowly over ca 20 mins with 1M lithium aluminium hydride in THF (259 ml, 259 mmol), keeping internal temperature below 15°C. When the addition was complete, the mixture was allowed to warm to room temperature and stirred for 2 hours, then heated at reflux for 2 hours. The mixture was allowed to cool to room temperature and was then cooled to ca -15°C in a dry ice/acetone bath and treated cautiously with a 2:1 mixture of THF-water (100 ml). When the addition was complete the mixture was treated with more water (220 ml) and then with 2M sodium hydroxide until a filterable solid was formed. This was removed by filtration and washed with ethyl acetate (500 ml). The filtrate was washed with brine (500 ml) and the aqueous phase extracted with ethyl acetate (2x 250 ml). The organic extracts were combined, dried (sodium sulphate) and evaporated to give the title compound as an off white crystalline solid. (42.9g)

MS (ES): $C_{10}H_{13}NO_2$ requires 179; found 180 $[M+H]^+$.

96

Preparation 85

2,3,4,5-tetrahydro-1,4-benzoxazepin-9-ol hydrobromide

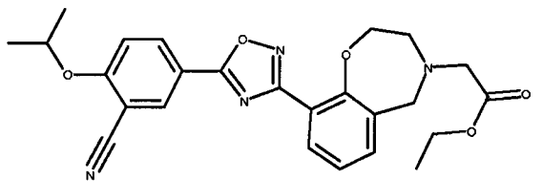


A suspension of 9-(methyloxy)-2,3,4,5-tetrahydro-1,4-benzoxazepine (Preparation 84) (43.4 g, 242 mmol) in 33% HBr in acetic acid (300 ml, 1823mmol) was heated at 80°C overnight. The mixture was allowed to cool to room temperature then treated with diethyl ether (300 ml) and stirred for 30 minutes. The resulting solid was collected by filtration, washed with diethyl ether (300 ml) and dried under vacuum at 40°C to give the title compound as a pale brown powder (55.1g)

MS (ES): $C_9H_{11}NO_2$ requires 165; found 166 $[M+H]^+$.

Preparation 86

Ethyl [9-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]acetate

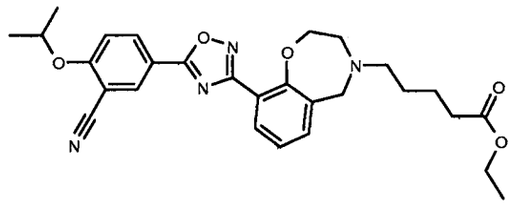


To a solution of 2-[(1-methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1,4-benzoxazepin-9-yl)-1,2,4-oxadiazol-5-yl]benzonitrile (Example 32) (110 mg, 0.224 mmol) in acetonitrile (10 mL) was added *N,N*-diisopropylethylamine (0.08 mL, 0.449 mmol) and ethyl bromoacetate (0.05 mL, 0.449 mmol). The reaction mixture was heated to 80°C for 2 hours. The mixture was allowed to cool to room temperature. The solvent was evaporated to give the title compound as a brown solid (100mg).

MS (ES) $C_{25}H_{26}N_4O_5$ requires 462 Found 463 $[M+H]^+$.

Preparation 87

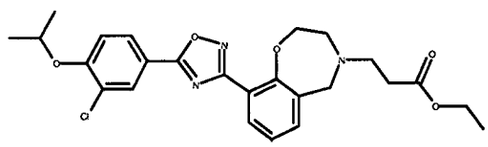
Ethyl 5-[9-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]pentanoate



To a solution of 2-[(1-methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1,4-benzoxazepin-9-yl)-1,2,4-oxadiazol-5-yl]benzonitrile (Example 32) (100 mg, 0.204 mmol) in acetonitrile (10 ml) was added *N,N*-diisopropylethylamine (0.07 ml, 0.408 mmol) and ethyl 5-bromopentanoate (0.06 mL, 0.408 mmol). The reaction mixture was heated to 80°C overnight then was allowed to cool and the solvent evaporated. Purification of the residue by flash chromatography, eluting with (40-100% ethyl acetate in cyclohexane) gave the title compound as an off white solid (70mg).
MS (ES) $C_{28}H_{32}N_4O_5$ requires 504 Found 505 $[M+H]^+$.

Preparation 88

Ethyl 3-[9-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propanoate

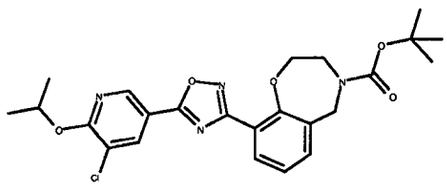


To a solution of 9-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrochloride (Example 31) (260 mg, 0.62 mmol) in acetonitrile (15 ml) was added *N,N*-diisopropylethylamine (0.214 ml, 1.23 mmol) followed by ethyl 3-bromopropanoate (0.158 ml, 1.231 mmol). The reaction mixture was heated at 80°C overnight. A further 1 equiv. of *N,N*-diisopropylethylamine and ethyl 3-bromopropanoate were added and heating continued overnight. The reaction mixture was cooled and evaporated. Purification of the residue by column chromatography, eluting with 50-65% ethyl acetate in cyclohexane to give the title compound as a yellow oil (80mg).

MS (ES) $C_{25}H_{28}{}^{35}ClN_3O_5$ requires 485 Found 486 $[M+H]^+$.

Preparation 89

1,1-Dimethylethyl 9-{5-{5-chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate

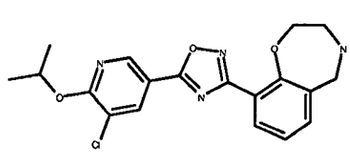


Triethylamine (0.281 ml, 2.02 mmol) was added to a stirred solution of 5-chloro-6-[(1-methylethyl)oxy]-3-pyridinecarboxylic acid (may be prepared as described in WO9702244; 217 mg, 1.01 mmol) in *N,N*-dimethylformamide (20 ml) followed by hydroxybenzotriazole hydrate (185 mg, 1.21 mmol) then 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (232 mg, 1.21 mmol) and lastly 1,1-dimethylethyl 9-[(hydroxyamino)(imino)methyl]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (Preparation 65) (310 mg, 1.009 mmol). The reaction mixture was heated to 60°C for 48 hours, then allowed to cool before diluting with ethyl acetate and washing with water. The organic phase was dried and evaporated. Purification of the residue by column chromatography, eluting with 15-25% ethyl acetate in cyclohexane to give the title compound as an amber coloured gum (280mg).

MS (ES) $C_{24}H_{27}{}^{35}ClN_4O_5$ requires 486 found 487 $[M+H]^+$.

Preparation 90

9-{5-{5-Chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrochloride.

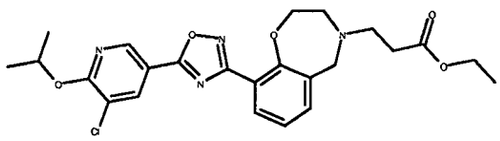


99

A mixture of1,1-dimethylethyl 9-(5-{5-chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (Preparation 89) (190 mg, 0.390 mmol), 4M hydrogen chloride in dioxane (1 ml, 4.00 mmol) and 1,4-dioxane (10 ml) was stirred at 60°C overnight. The reaction mixture was cooled and a white precipitate formed. The solid was filtered off to give the product as a white solid (170mg). MS (ES) $C_{19}H_{19}{}^{35}ClN_4O_3$ requires 386 Found 387 $[M+H]^+$.

Preparation 91

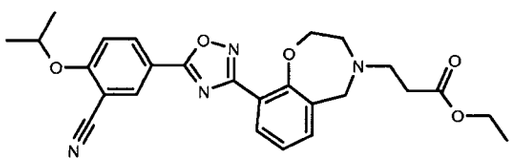
Ethyl 3-[9-(5-{5-chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propanoate



To a solution of 9-(5-{5-chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrochloride (Preparation 90) (80 mg, 0.189 mmol) in acetonitrile (10 ml) was added *N,N*-diisopropylethylamine (0.066 ml, 0.378 mmol) followed by ethyl 3-bromopropanoate (0.048 ml, 0.378 mmol). The reaction mixture was heated at 80°C overnight. A further 1 equivalent of *N,N*-diisopropylethylamine and ethyl 3-bromopropanoate were added and heating continued overnight. The reaction mixture was cooled and evaporated. The residue was purified by column chromatography on silica. Elution with 40-60% ethyl acetate in cyclohexane to give the title compound as an olive green coloured oil (28mg).
MS (ES) $C_{24}H_{27}{}^{35}ClN_4O_5$ requires 486 Found 487 $[M+H]^+$.

Preparation 92

Ethyl 3-[9-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propanoate



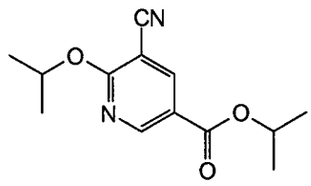
100

To a solution of 2-[(1-methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1,4-benzoxazepin-9-yl)-1,2,4-oxadiazol-5-yl]benzonitrile hydrochloride (Example 32) (90 mg, 0.218 mmol) in acetonitrile (10 ml) was added *N,N*-diisopropylethylamine (0.076 ml, 0.436 mmol) followed by ethyl 3-bromopropanoate (0.056 ml, 0.436 mmol). The reaction mixture was heated at 80°C overnight. A further 1 equivalent of *N,N*-diisopropylethylamine and ethyl 3-bromopropanoate were added and heating continued overnight. The reaction mixture was cooled and evaporated. Purification of the residue by column chromatography on silica, eluting with 60-70% ethyl acetate in cyclohexane to give the title compound as a brown oil (40mg).

MS (ES) $C_{10}H_{13}NO_2$ requires 476 Found 477 $[M+H]^+$.

Preparation 93

1-Methylethyl 5-cyano-6-[(1-methylethyl)oxy]-3-pyridinecarboxylate



A mixture of 1-methylethyl 5-chloro-6-[(1-methylethyl)oxy]-3-pyridinecarboxylate (may be prepared as described in WO9702244; 7.73 g, 30.0 mmol) in dry *N,N*-dimethylformamide (DMF) (60 ml) and zinc cyanide (4.23 g, 36.0 mmol) at room temperature was de-gassed and flushed with nitrogen several times. Tetrakis(triphenylphosphine)palladium(0) (3.47 g, 3.00 mmol) was added and the degassing procedure repeated. The reaction mixture was then heated to 100 °C for 24hrs. The reaction mixture was allowed to cool to room temperature, then filtered to remove solid residues, washing with a little DMF. A further quantity of zinc cyanide (4.23 g, 36.0 mmol) and a different batch of tetrakis(triphenylphosphine)palladium(0) (3.47 g, 3.00 mmol) were added, with the same de-gassing and nitrogen flush. Heating was then continued at 100 °C for 2hr.

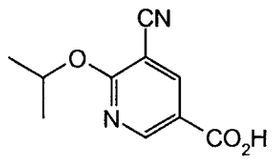
The reaction mixture was allowed to cool to room temperature again, diluted with ethyl acetate and filtered to remove the solid residues. The solution was concentrated to an oil. On standing, more solid separated. The mixture was extracted with ethyl acetate, then the organic phase washed with water (2x), brine, dried and concentrated to an orange oil. The crude material was loaded onto a silica gel column and chromatographed, eluting with a gradient of 0-10% ethyl acetate in cyclohexane to give 3.87g of product still contaminated with triphenylphosphine. Further purification by chromatography, eluting with a gradient of 0-5% ethyl acetate

101

in cyclohexane gave the title compound (1.32g),
MS (ES) $C_{13}H_{16}N_2O_3$ requires 248; found 248 $[M+H]^+$.

Preparation 94

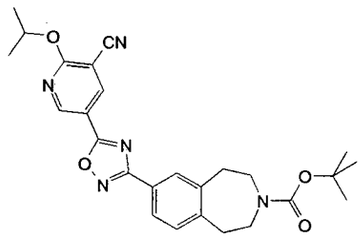
5-Cyano-6-[(1-methylethyl)oxy]-3-pyridinecarboxylic acid



1-Methylethyl 5-cyano-6-[(1-methylethyl)oxy]-3-pyridinecarboxylate (Preparation 93) (1.28g, 5.15 mmol) in ethanol (20 ml) was treated with sodium hydroxide (5.15 ml, 10.30 mmol) and the mixture stirred at room temperature to give a homogeneous solution, until LC/MS showed no starting material. The mixture was concentrated to remove ethanol. The residue was diluted with water, then acidfied with 2M HCl to give a thick white precipitate. The solid was filtered off, washed with water and dried overnight *in vacuo* at 60°C, to give the title compound (1.07g),
MS (ES) $C_{10}H_{10}N_2O_3$ requires 206; found 205 $[M-H]^+$.

Preparation 95

1,1-Dimethylethyl 7-(5-{5-cyano-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate



A solution of 5-cyano-6-[(1-methylethyl)oxy]-3-pyridinecarboxylic acid (Preparation 94) (206 mg, 0.999 mmol) in dichloromethane (5 ml) at room temperature was treated with oxalyl chloride (0.262 ml, 3.00 mmol) and 1 drop of *N,N*-dimethylformamide (DMF). After 1hr, the solution was concentrated to give the crude acid chloride as a yellow gum.

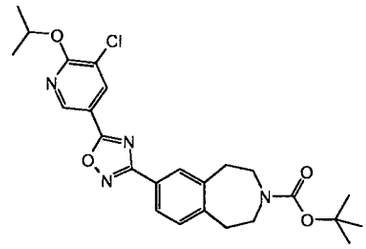
1,1-Dimethylethyl 7-[(hydroxyamino)(imino)methyl]-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (Preparation 41) (305 mg, 0.999 mmol) in DMF (5.00 ml) was treated with triethylamine (0.17 ml, 1.20 mmol) followed by the crude acid chloride (described above) in DMF (1ml). After 10mins the mixture was heated to 120 °C. After 2hrs the reaction mixture was allowed to cool to room temperature and

102

concentrated. The residue was partitioned between ethyl acetate and dilute sodium hydroxide. The organic layer was washed with brine, dried and concentrated to give a yellow gum, which crystallised on standing. The crude material was loaded onto a silca gel column and chromatographed eluting with a gradient of 0-20% ethyl acetate in cyclohexane to give the title compound as a colourless crystalline solid (224mgs), MS (ES) $C_{26}H_{29}N_5O_4$ requires 475; found 420 $[M+ -tBu]^+$.

Preparation 96

1,1-Dimethylethyl 7-{5-{5-chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate



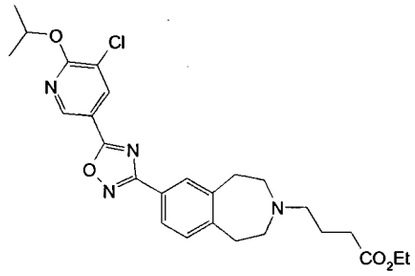
A suspension of 5-chloro-6-[(1-methylethyl)oxy]-3-pyridinecarboxylic acid (may be prepared as described in WO9702244; 215 mg, 0.999 mmol) in dichloromethane (3 ml) at room temperature was treated with oxalyl chloride (0.26 ml, 3.00 mmol) and 1 drop of *N,N*-dimethylformamide (DMF). After 2hrs the solution was concentrated to give the crude acid chloride as a yellow oil.

1,1-Dimethylethyl 7-[(hydroxyamino)(imino)methyl]-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (Preparation 41) (305 mg, 0.999 mmol) was dissolved in dry DMF (2 ml), treated with triethylamine (0.17 ml, 1.20 mmol) and stirred at room temperature. A solution of the crude acid chloride (described above) in dry DMF (2 ml) was added to give a pale yellow, turbid solution. The mixture was stirred for 1.5hr at room temperature, then heated to 120 °C for 2hrs. The reaction mixture was allowed to cool to room temperature, and concentrated. The residue was partitioned between ethyl acetate and water. The organic layer was washed with water then brine, dried and concentrated to a cream foam. The crude material was loaded onto a silica gel column and chromatographed eluting with a gradient of 0-15% ethyl acetate in cyclohexane to give title compound was obtained as a colourless foam/solid, (305mgs), MS (ES) $C_{25}H_{29}{}^{35}ClN_4O_4$ requires 484; found 429 $[M+ -tBu]^+$.

Preparation 97

163

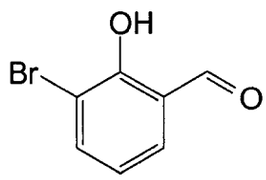
Ethyl 4-[7-(5-{5-chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoate



7-(5-{5-Chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (Example 50) (192 mg, 0.499 mmol) in *N,N*-dimethylformamide (2 ml) at room temperature was treated with potassium carbonate (103 mg, 0.748 mmol) and ethyl 4-bromobutanoate (0.09 ml, 0.60 mmol). The mixture was heated to 100 °C. After *ca.* 2hrs, the mixture was cooled and concentrated. The residue was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with brine, dried and concentrated to a colourless gum. The crude material was loaded onto a silica gel column and chromatographed, eluting with a gradient of 80-100% ethyl acetate in cyclohexane gave the title compound as a colourless gum, which slowly crystallized on standing (185mgs).
MS (ES) $C_{26}H_{31}{}^{35}ClN_4O_4$ requires 498; found 499 $[M+H]^+$.

Preparation 98

3-Bromo-2-hydroxybenzaldehyde

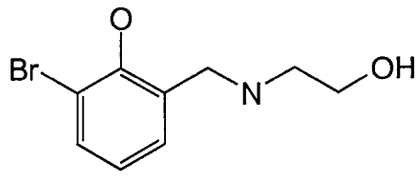


Triethylamine (72 ml, 520 mmol) was added over 10 minutes to a suspension of paraformaldehyde (23.4 g, 780 mmol) and dry magnesium dichloride (49.5 g, 520 mmol, Aldrich; CAS 7786-30-3) in THF (1 litre) under nitrogen at room temperature. The resulting mixture was stirred for 20 min, then 2-bromophenol (45 g, 260 mmol) was added over 5 minutes via syringe. The resulting mixture was stirred under gentle reflux for 6 h then cooled to room temperature. The solution was left over the weekend and then diluted with diethylether (500 ml). The organic phase was washed

with a 2N hydrochloric acid (500 ml) and the two phases were separated. The insoluble material was filtered off and the organic phase was washed twice with 2N hydrochloric acid (500 ml) then five times with water (100 ml), dried over magnesium sulphate and concentrated *in vacuo* to give the title compound as a colourless solid (46.5 g). MS (ES) $C_7H_5{}^{79}BrO_2$ requires 200 found 199 $[M-H]^+$.

Preparation 99

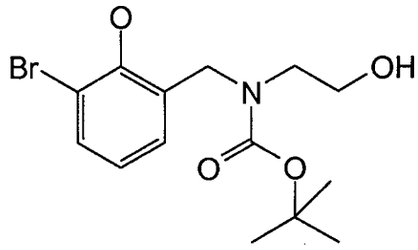
2-Bromo-6-{[(2-hydroxyethyl)amino]methyl}phenol



To a solution of 3-bromo-2-hydroxybenzaldehyde (Preparation 98) (9.6 g, 47.8 mmol) in tetrahydrofuran (250 ml) at 0°C under nitrogen was added 2-aminoethanol (3.02 ml, 50.1 mmol) then finely powdered sodium triacetoxyborohydride (10.6 g, 50.1 mmol) and the resulting mixture was stirred at 0°C for 1 h, then stirred overnight and concentrated in vacuo. The residue was triturated under dichloromethane (~200mL) and insoluble material was filtered off. The organic phase was concentrated *in vacuo* and the residue purified using an SCX column to give the title compound as a white solid (10.1 g,). MS (ES) $C_9H_{10}{}^{79}BrNO_2$ requires 243 found 244 $[M+H]^+$.

Preparation 100

1,1-Dimethylethyl [(3-bromo-2-hydroxyphenyl)methyl](2-hydroxyethyl)carbamate

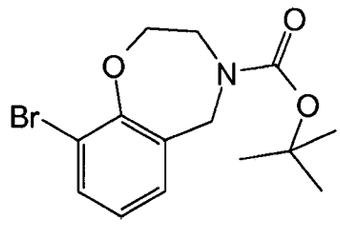


2-Bromo-6-{[(2-hydroxyethyl)amino]methyl}phenol (Preparation 99) (2.3 g, 9.35 mmol) was dissolved in methanol (10 ml) and tetrahydrofuran (40 ml) and the resulting mixture was cooled at 0°C. Triethylamine (1.95 ml, 14.0 mmol), then bis(1,1-dimethylethyl) dicarbonate (2.39 ml, 10.3 mmol) were added and the resulting mixture stirred at this temperature for 2.5 h. Further triethylamine (195 ml, 1.40 mmol) and bis(1,1-dimethylethyl) dicarbonate (239 ml, 1.03 mmol) were added and the resulting mixture was allowed to warm to room temperature and left to stand over

the weekend then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and the organic phase was washed twice with a 2N hydrochloric acid then brine and dried (magnesium sulphate) and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel, eluting with 15-45% ethyl acetate in cyclohexane gave the title compound as a pale yellow oil (3.4 g,). MS (ES) $C_{14}H_{20}{}^{79}BrNO_4$ requires 345 found 246 $[M+H-COOC(CH_3)_3]^+$.

Preparation 101

1,1-Dimethylethyl 9-bromo-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate



A mixture of 1,1-dimethylethyl [(3-bromo-2-hydroxyphenyl)methyl](2-hydroxyethyl)carbamate (Preparation 100) (2.35 g, 6.79 mmol) and triphenylphosphine (1.96 g, 7.47 mmol) in tetrahydrofuran (40 ml) under nitrogen was cooled to 0°C. Diisopropyl azodicarboxylate (DIAD) (1.47 ml, 7.47 mmol) was added dropwise and the resulting mixture stirred for 1h then concentrated *in vacuo*. The solvent was removed and the material washed twice with brine, dried (magnesium sulphate) then concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel, eluting with 5-25% ethyl acetate in cyclohexane gave the title compound (1.35g). MS (ES) $C_{14}H_{18}{}^{79}BrNO_2$ requires 327 found 228 $[M+H-COOC(CH_3)_3]^+$.

Alternative procedure (from 3-bromo-2-hydroxybenzaldehyde):

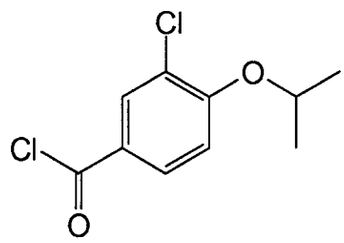
3-Bromo-2-hydroxybenzaldehyde (Aldrich; 5.0 g, 24.9 mmol) in ethanol (100 ml) at room temperature was treated with ethanolamine (1.65 ml, 27.4 mmol) and the resulting mixture was stirred for about 1 h. Sodium borohydride (1.129 g, 29.8 mmol) was then added and the resulting mixture heated under reflux for about 2 h then cooled to room temperature and then placed in ice-water, treated with triethylamine (5.2 ml, 37.3 mmol) followed by the portionwise addition of bis(1,1-dimethylethyl) dicarbonate (8.14 g, 37.3 mmol). Once the addition was complete, the resulting mixture was removed from the ice bath and the mixture stirred at room temperature for 30mins-1 h. The resulting mixture was treated with 2M sodium hydroxide (49.7 ml, 99 mmol) and stirred at 50°C for 1.5 h, at room temperature overnight, then at

106

60°C for 5 h. 2M Sodium hydroxide (49.7 ml, 99 mmol) was added and the resulting mixture stirred at 60°C for 2 h then at room temperature over the weekend. Most of the ethanol was removed *in vacuo* and the resulting aqueous phase acidified to pH 5 with 2N hydrochloric acid. The aqueous phase was extracted three times with dichloromethane and the organic phase washed with brine, dried (magnesium sulphate) and concentrated *in vacuo*. The residue was dissolved in tetrahydrofuran (100 ml) and treated at room temperature with triphenylphosphine (10.44 g, 39.8 mmol) followed by the dropwise addition of diisopropyl azodicarboxylate (DIAD) (7.74 ml, 39.8 mmol). The resulting mixture was briefly cooled using ice-water and then stirred for 1-2 h at room temperature then concentrated in vacuo. The crude material in DCM was loaded onto fine silica in a sinter funnel, washed through with cyclohexane(200mLs), followed by 3x 500mL portionsof 10%EtOAc/cyclohexane. Each portion was concentrated separately. Purification of the residue by flash chromatography on silica gel, eluting with 0-10% ethyl acetate in cyclohexane gave the title compound (6.62 g). MS (ES) $C_{14}H_{18}{}^{79}BrNO_2$ requires 327 found 228 [M+H-$COOC(CH_3)_3$]$^+$.

Preparation 102

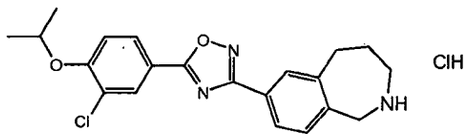
3-Chloro-4-[(1-methylethyl)oxy]benzoyl chloride



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). δH (CDCl3, 400MHz): 1.44 (6H, d), 4.73 (1H, septet), 6.98 (1H, d), 8.0 (1H, dd), 7.98 (1H, d).

Example 1

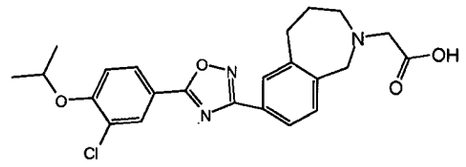
7-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1H-2-benzazepine hydrochloride



1,1-Dimethylethyl 7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepine-2-carboxylate (Preparation 7) (75mg, 0.155 mmol) was treated with 4N HCl in dioxan (1162 µl, 4.65 mmol) and the clear solution left standing for 1.5 hours. A white precipitate formed. Ether (1ml) was added and the white solid was filtered off, washing with ether. The title compound was obtained on drying of the solid (45 mg). δH (400 MHz, d_6DMSO) 1.36 (6H, d), 1.91-1.98 (2H, m), 3.11-3.14 (2H, m), 3.36-3.39 (2H, m), 4.41 (2H, s), 4.85-4.94 (1H, m), 7.46 (1H, d), 7.64 (1H, d), 7.95-7.80 (2H, m), 8.11 (1H, dd), 8.19 (1H, d), 9.04 (2H, broad s); MS (ES) $C_{21}H_{22}{}^{35}ClN_3O_2$ requires 383; found 384.0 $[M+H]^+$.

Example 2

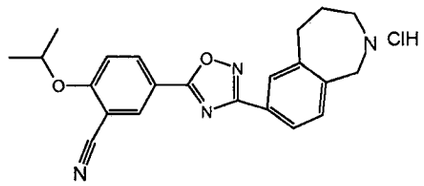
[7-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]acetic acid



1,1-Dimethylethyl [7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]acetate (Preparation 8) (65mg, 0.131 mmol) was treated with HCl (1305 µl, 5.22 mmol) (4N in dioxan) and left standing for 2 hours. The reaction mixture was then warmed at 50 °C for 1 hour then heated at 60 °C for a further 1.25 hours before solvent removal by evaporation. Trituration with ether/EtOAc failed and the material obtained was purified by MDAP. A white solid (20mg) was obtained freeze drying appropriate MDAP fractions. Further drying under vacuum at 70 °C for 16 hours yielded the title compound (16 mg) as a solid. δH (400 MHz, d_6DMSO) 1.36 (6H, d), 1.51-1.53 (2H, m), 2.98-3.00 (2H, m), 3.4 (2H, br.s), 4.10 (2H, s), 4.86-4.92 (1H, m), 7.32 (1H, d), 7.44 (1H, d), 7.83-7.88 (2H, m), 8.11 (1H, dd), 8.18 (1H, d); MS (ES) $C_{23}H_{24}{}^{35}ClN_3O_4$ requires 441; found 442 $[M+H]^+$.

Example 3

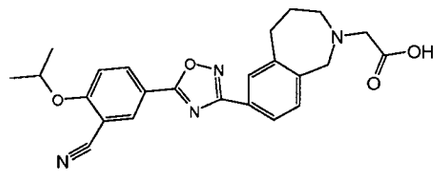
2-[(1-Methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1H-2-benzazepin-7-yl)-1,2,4-oxadiazol-5-yl]benzonitrile hydrochloride



1,1-Dimethylethyl 7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepine-2-carboxylate (Preparation 9) (310mg, 0.653 mmol) was treated with HCl (3266 µl, 13.06 mmol) (4N in dioxan) and stirred. After 30 minutes a white precipitate had formed. After 1 hour ether (2ml) was added and the precipitate filtered off and washed with ether. The title compound (230mg) was obtained on drying. δH (400 MHz, d_6DMSO) 1.39 (6H, d), 1.91 (2H, m), 3.11-3.13 (2H, m), 3.37-3.40 (2H, m), 4.42 (2H, s), 4.94-5.02 (1H, m), 7.57 (1H, d), 7.64 (1H, d), 7.96-8.00 (2H, m), 8.41 (1H, dd), 8.52 (1H, d), 9.04 (2H, broad s); MS (ES) $C_{22}H_{22}N_4O_2$ requires 374; found 375.0 $[M+H]^+$.

Example 4

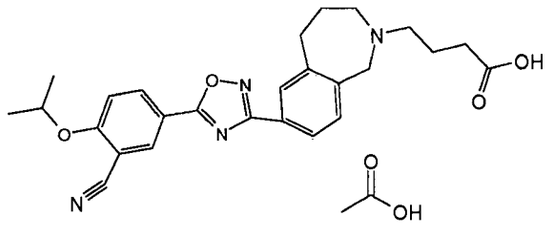
[7-(5-{3-Cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]acetic acid



1,1-Dimethylethyl [7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]acetate (Preparation 10) (85mg, 0.174 mmol) was treated with HCl (1305 µl, 5.22 mmol) (4N soln in dioxan) and warmed at 50 °C for 2 hours. A white crystalline product formed. The reaction was cooled to RT and the solid filtered off and washed with ether. On drying the title compound was obtained (65mg) as a white solid. δH (400 MHz, d_6DMSO) 1.39 (6H, d), 1.91-2.00 (2H, m), 3.11-3.12 (2H, m), 3.59 (2H, m), 4.00 (2H, s), 4.60 (2H, s), 4.94-5.02 (1H, m), 7.53-7.59 (2H, m), 7.99-8.06 (2H, m), 8.41 (1H, dd), 8.52 (1H, d); MS (ES) $C_{24}H_{24}N_4O_4$ requires 432; found 433 $[M+H]^+$.

Example 5

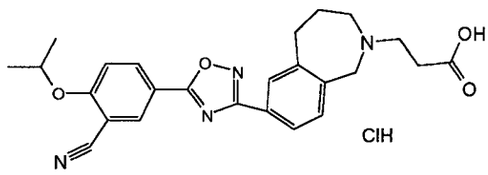
4-[7-(5-{3-Cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]butanoic acid acetate



Ethyl 4-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]butanoate (preparation 11) (90mg, 0.184 mmol) dissolved in ethanol (20ml) was treated with sodium hydroxide (0.184 ml, 0.368 mmol) (2N (aq)) solution followed by water (5.00 ml). This mixture was stirred at RT for 3 hours and left standing overnight. 2N NaOH (aq) (150 µl) was added and the reaction mixture stirred for 3 hours. Then ethanol was removed by evaporation and the aqueous layer acidified using AcOH. The product was extracted into EtOAc (50ml) and dried over $MgSO_4$. Solvent removal by evaporation yielded a white precipitate. Ether was added and the solid filtered off and washed with ether to yield the title compound (44mg) on drying. δH (400 MHz, d_6DMSO) 1.39 (6H, d), 1.91-1.95 (4H, m), 2.30 (2H, t), 2.96 (2H, m), 3.13 (2H, m), 3.53 (2H, m), 4.60 (2H, s), 4.94-5.03 (1H, m), 7.57 (1H, d), 7.68 (1H, d), 7.97-8.00 (2H, m), 8.41 (1H, dd), 8.52 (1H, d) 10.6 (1H, v. broad s), 12.3 (1H, v. broad s); MS (ES) $C_{26}H_{28}N_4O_4$ requires 460; found 461.0 $[M+H]^+$.

Example 6

3-[7-(5-{3-Cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]propanoic acid hydrochloride

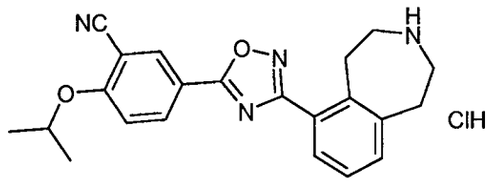


1,1-Dimethylethyl 3-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]propanoate (Preparation 12) (70mg, 0.139 mmol) was treated with HCl (1045 µl, 4.18 mmol) (4N in dioxan) and warmed at 50 °C for 1.5 hours. A white precipitate started to form. Ether (0.5ml) was added and the white solid filtered off and washed with ether to give the title compound (57mg) on drying. δH (400 MHz, d_6DMSO) 1.39 (6H, d), 1.91-1.96 (2H, m), 2.82 (2H, m), 3.12-3.21 (4H, m), 3.56 (2H, m), 4.62 (2H, s), 4.96-5.02 (1H, m), 7.57 (1H, d), 7.71 (1H, d), 7.99-8.01 (2H, m), 8.41 (1H, dd), 8.52 (1H, d), 10.3 (1H, v. broad s), 12.8 (1H, v. broad s); MS (ES) $C_{25}H_{26}N_4O_4$ requires 446; found 447.0 $[M+H]^+$.

110

Example 7

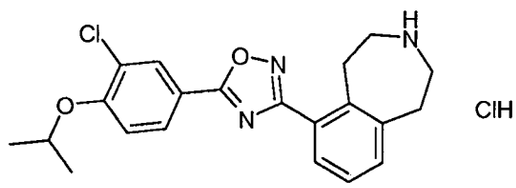
2-[(1-Methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1H-3-benzazepin-6-yl)-1,2,4-oxadiazol-5-yl]benzonitrile hydrochloride



1,1-Dimethylethyl 6-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (Preparation 16) (505 mg, 1.064 mmol) was dissolved in DCM (40 ml) and treated with trifluoroacetic acid (4 ml, 51.9 mmol). The resulting mixture was heated at reflux for 1 hour then evaporated. The resulting residue was partitioned between DCM (20ml) and 2N NaOH (20ml). The DCM layer was collected, dried (hydrophobic frit) and evaporated. The free-base was dissolved in 4M HCl in dioxane and evaporated to give the HCl salt, 2-[(1-methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1H-3-benzazepin-6-yl)-1,2,4-oxadiazol-5-yl]benzonitrile hydrochloride (438 mg, 1.066 mmol, 100 % yield) as an off-white powder. δH (400 MHz, $CDCl_3$) 10.15 (1H, br.s), 8.39 (1H, s), 8.33-8.31 (1H, m), 7.75-7.85 (1H, m), 7.45-7.3 (2H, m), 7.14 (1H, d), 4.84-4.76 (1H, m), 3.90-3.30 (8H, m) 1.48 (6H, d); MS (ES) $C_{22}H_{22}N_4O_2$ requires 374; found 375 $[M+H]^+$.

Example 8

6-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride

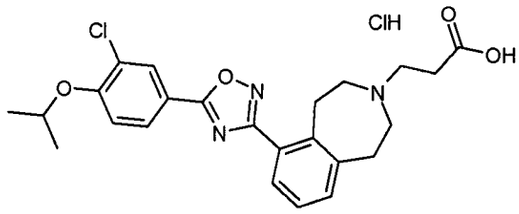


1,1-Dimethylethyl 6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (Preparation 17) (260 mg, 0.537 mmol) was dissolved in DCM (20 ml) and treated with trifluoroacetic acid (2 ml, 26.0 mmol). The resulting mixture was heated at reflux for 1 hour then evaporated. The resulting residue was partitioned between DCM (10ml) and 2N NaOH (10ml). The DCM layer was collected, dried (hydrophobic frit) and evaporated. The free-base was dissolved in 4M HCl in dioxane and evaporated to give the HCl salt, 6-(5-{3-chloro-4-

[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (225 mg, 0.535 mmol, 100 % yield) as an off-white powder. δH (400 MHz, $CDCl_3$) 10.10 (2H, br.s), 8.18 (1H, s), 8.02 (1H, d), 7.82-7.80 (1H, m), 7.33-7.22 (2H, m), 7.05 (1H, d), 5.30 (2H, s), 4.76-4.64 (1H, m), 3.8-3.65 (2H, m), 3.48-3.3 (4H, m), 1.45 (6H, d); MS (ES) $C_{21}H_{22}{}^{35}ClN_3O_2$ requires 383; found 384 $[M+H]^+$.

Example 9

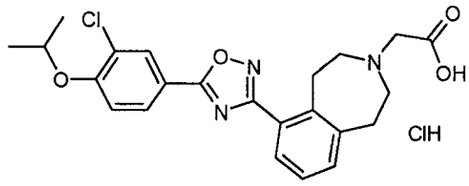
3-[6-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]propanoic acid hydrochloride



1,1-Dimethylethyl 3-[6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]propanoate (Preparation 18) (25 mg, 0.049 mmol) was stirred at room temperature for 18 hours in 4M HCl in 1,4-dioxane (10 ml). Evaporation and trituration with diethylether yielded the title compound 3-[6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]propanoic acid hydrochloride (13 mg, 0.026 mmol, 54.1 % yield) as a yellow gum. MS (ES) $C_{24}H_{26}{}^{35}ClN_3O_4$ requires 455; found 456 $[M+H]^+$.

Example 10

[6-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]acetic acid hydrochloride



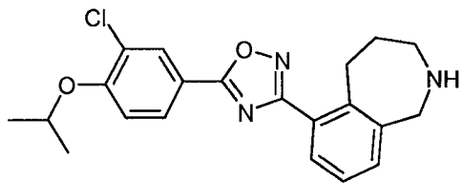
1,1-Dimethylethyl [6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]acetate (Preparation 19) (120 mg, 0.241 mmol) was stirred at room temperature for 18 hours in 4M HCl in 1,4-dioxane (20 ml). Evaporation and trituration with diethylether yielded the HCl salt [6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-

112

benzazepin-3-yl]acetic acid hydrochloride (110 mg, 0.216 mmol, 90 % yield) as a cream powder. MS (ES) $C_{23}H_{24}{}^{35}ClN_3O_4$ requires 441; found 442 $[M+H]^+$.

Example 11

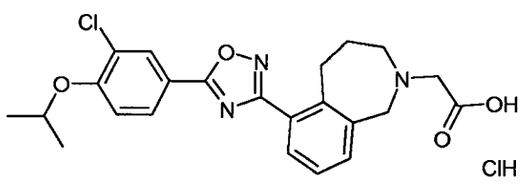
6-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine



To a solution of 3-[2-(aminomethyl)-6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)phenyl]-1-propanol (Preparation 23) (105.2 mg, 0.262 mmol) and triphenylphosphine (343 mg, 1.309 mmol) in dry DCM (40 ml) at RT under Ar was added DIAD (0.242 ml, 1.243 mmol) dropwise and the resulting pale yellow solution stirred at RT for 18 hrs. The solution was concentrated to ~5 ml, then passed down an SCX-3 cartridge (1 g), washing with MeOH. The product was eluted with 0.5M NH_3 in MeOH; concentration in vacuo gave a pale yellow oil (95.7 mg). Reverse-phase mass-directed auto-purification gave two fractions containing the desired product, one of which was contaminated with $O=PPh_3$. Both were added directly to an SCX-2 cartridge (10 g), washing with MeOH. The product was eluted with 0.5M NH_3 in MeOH; concentration in vacuo gave a pale yellow film 6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1*H*-2-benzazepine (15.3 mg, 0.034 mmol, 12.94 % yield). δH (400 MHz, $CDCl_3$) 8.20 (1H, d), 8.04 (1H, dd), 7.69 (1H, d), 7.31 (1H, d), 7.24 (1H, t), 7.05 (1H, d), 4.71 (1H, sept), 4.09 (2H, s), 3.30-3.24 (4H, m), 1.80 (2H, m), 1.44 (6H, d); MS (ES) $C_{21}H_{22}{}^{35}ClN_3O_2$ requires 383; found 384 $[M+H]^+$.

Example 12

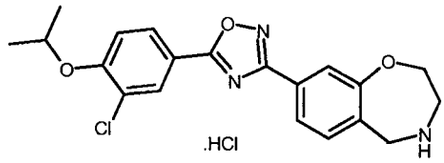
[6-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]acetic acid hydrochloride



A 5:2 mixture of 1,1-dimethylethyl [6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]acetate and [6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]acetic acid (Preparation 24) (21.4mg) in 4M HCl in dioxane (3 ml) was stirred at RT for 21 hours. The reaction mixture was concentrated in vacuo, then redissolved in 4M HCl in dioxane (3 ml), and the solution stirred for an additional 24 hours. Concentration in vacuo gave a yellow oil (41 mg), that was triturated with ether (2 x 3 ml) to leave a white solid [6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]acetic acid hydrochloride (16.1 mg, 0.031 mmol, 90 % yield). δH (400 MHz, d_6DMSO) 8.17 (1H, d), 8.10 (1H, dd), 7.87 (1H, dd), 7.58 (1H, d), 7.49 (1H, t), 7.46 (1H, d), 4.89 (1H, sept), 4.69 (2H, s), 4.06 (2H, s), 3.58 (2H, br t), 3.35 (2H, m), 2.00 (2H, br s), 1.36 (6H, d); MS (ES) $C_{23}H_{24}{}^{35}ClN_3O_4$ requires 441; found 442 $[M+H]^+$.

Example 13

8-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrochloride

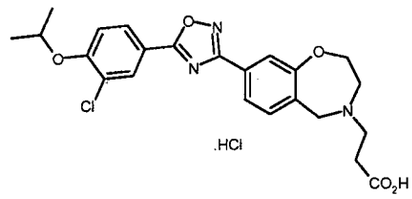


1,1-Dimethylethyl 8-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (Preparation 34) (0.171 g, 0.352 mmol) was dissolved in 1,4-dioxane (1 ml) and 4M HCl (4 ml, 16.00 mmol) in dioxane was added. The reaction mixture was left at room temperature for 3 hours. The resulting precipitated solid was filtered off and washed with dioxane and ether to give the title compound (116mgs) as a white solid hydrochloride salt. δH (400 MHz, MeOD) 1.42 (6H, d), 3.64 (2H, m), 4.34 (2H, m), 4.48 (2H, s), 4.86 (1H, m), 7.31 (1H, d), 7.59 (1H, d), 7.87 (1H, d), 7.94 (1H, dd), 8.11 (1H, dd), 8.21 (1H, dd); MS (ES) $C_{20}H_{20}{}^{35}ClN_3O_3$ requires 385; found 486 $[M+H]^+$.

Example 14

3-[8-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]propanoic acid hydrochloride

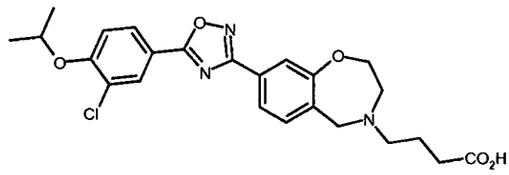
114



2M Sodium hydroxide solution (aq) (0.5 ml, 1.000 mmol) was added to a solution of ethyl 3-[8-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propanoate (Preparation 35) (0.09 g, 0.185 mmol) in ethanol (4 ml) and left at room temperature for 2 hours. The reaction was then evaporated and the resulting crude dissolved in EtOAc/water (30ml of each) and acidified with acetic acid. The organic layer was dried (magnesium sulphate) and evaporated. The resulting crude was azeotroped with 20ml of toluene and the residue dissolved in 10ml of DCM. 1M HCl (1ml) in ether was added, the reaction mixture evaporated then triturated with ether. The title compound (56mg) was filtered off as an off-white solid hydrochloride salt. δH (400 MHz, MeOD) 1.42 (6H, d), 2.92 (2H, t), 3.55 (2H, t), 3.78 (2H, m), 4.40 (2H, m), 4.65 (2H, s), 4.87 (1H, m), 7.31 (1H, d), 7.61 (1H, d), 7.87 (1H, d), 7.96 (1H, dd), 8.11 (1H, dd), 8.21 (1H, d); MS (ES) $C_{23}H_{24}{}^{35}ClN_3O_5$ requires 457; found 458 $[M+H]^+$.

Example 15

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



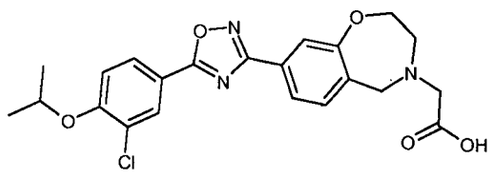
2M Sodium hydroxide (aq) (0.5 ml, 1.000 mmol) was added to a solution of ethyl 4-[8-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]butanoate (Preparation 36) (0.103 g, 0.206 mmol) in ethanol (4 ml) and left at room temperature for 2 hours. The reaction mixture was evaporated and the residue dissolved in water/EtOAc (30ml of each) and acidified with acetic acid. The organic layer was collected, dried (magnesium sulphate), evaporated and azeotroped with 15ml of toluene. The title compound was obtained by triturating with ether and filtering off as a white solid (65mg). δH (400 MHz, d_6DMSO) 1.36 (6H, d), 1.70 (2H, m), 2.23 (2H, t), 2.33 (2H, t), 3.02 (2H, m), 3.84 (2H, s), 4.06 (2H, m), 4.89

115

(1H, m), 7.44 (2H, m), 7.61 (1H, d), 7.72 (1H, dd), 8.10 (1H, dd), 8.18 (1H, d); MS (ES) $C_{24}H_{26}{}^{35}ClN_3O_5$ requires 471; found 472 $[M+H]^+$.

Example 16

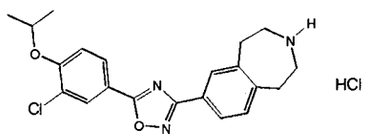
[8-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]acetic acid



1,1-Dimethylethyl [8-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]acetate (Preparation 37) (0.13 g, 0.260 mmol) was dissolved in 1,4-dioxane (1 ml) and 4M HCl (4 ml, 16.00 mmol) in dioxan was added and the reaction mixture was left at room temperature for 24 hours. Then the reaction mixture was evaporated, triturated with ether and the resulting solid filtered off. The solid was dissolved in 5ml of 2M sodium hydroxide and acidified with acetic acid when solid separated. Attempted to dissolve in EtOAc but insoluble so filtered off and washed well with water, acetone and ether to give the title compound (44mgs) as a white solid. δH (400 MHz, d_6DMSO) 1.36 (6H, d), 3.13 (2H, br. s), 3.96 (2H, s), 4.08 (2H, br. s), 4.89 (1H, m), 7.38 (1H, d), 7.44 (1H, d), 7.61 (1H, s), 7.72 (1H, d), 8.11 (1H, d), 8.18 (1H, d), (remaining 2H signal obscured by solvent peak) ; MS (ES) $C_{22}H_{22}{}^{35}ClN_3O_5$ requires 443; found 444 $[M+H]^+$.

Example 17

7-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride

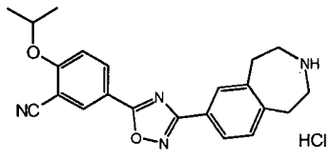


A solution of 1,1-dimethylethyl 7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (Preparation 42) (950 mg, 1.963 mmol) in hydrochloric acid (a 4M solution in dioxane, 10 ml, 40.0 mmol) and 1,4-dioxane (10 ml) was stirred at room temperature for 5 hours (a precipitate had formed). The reaction mixture was filtered and washed with dioxane (~5ml), and the solid dried under vaccum (pistol) overnight to yield the title compound (711 mg, 1.607 mmol, 82 % yield) as a white solid. δH ($CDCl_3$, 400 MHz):

10.17 (2H, br s), 8.25 (1H, d), 8.06 (1H, dd), 7.98-8.03 (2H, m), 7.33 (1H, d), 7.06 (1H, d), 4.72 (1H, sept), 3.35-3.47 (8H, m), 1.46 (6H, d). MS (ES): $C_{21}H_{22}{}^{35}ClN_3O_2$ requires 383; found 384 $[M+H]^+$.

Example 18

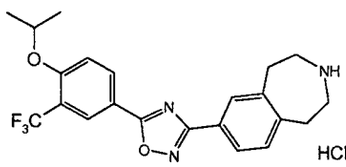
2-[(1-Methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1,2,4-oxadiazol-5-yl]benzonitrile hydrochloride



1,1-Dimethylethyl-7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (Preparation 43) (735 mg, 1.55 mmol) was dissolved in 4M HCl in dioxane and the solution stirred for 1 h. The title compound was filtered off as a white solid and dried in a vacuum oven (462 mg, 1.13 mmol). δH (d_6DMSO, 400 MHz): 9.24 (2H, brs), 8.51 (1H, d), 8.40 (1H, dd), 7.95 (1H, d), 7.92 (1H, dd), 7.57 (1H, d), 7.45 (1H, d), 4.98 (1H, septet), 3.28-3.18 (8H, m), 1.39 (6H, d). MS (ES): $C_{22}H_{22}N_4O_2$ requires 374; found 375 $[M+H]^+$.

Example 19

7-{5-[4-[(1-Methylethyl)oxy]-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride

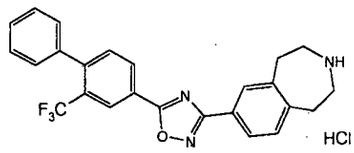


1,1-Dimethylethyl-7-{5-[4-[(1-methylethyl)oxy]-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (Preparation 44) (550 mg, 1.06 mmol) was dissolved in 4M HCl in dioxane (5 ml) and the solution stirred for 2 h. The title compound was filtered off as a white solid and dried in a vacuum oven (259 mg, 0.57 mmol). δH (d_6DMSO, 400 MHz): 9.23 (2H, brs), 8.40 (1H, dd), 8.31 (1H, d), 7.96 (1H, d), 7.93 (1H, dd), 7.59 (1H, d), 7.44 (1H, d), 4.98 (1H, septet), 3.27-3.18 (8H, m), 1.36 (6H, d); MS (ES): $C_{22}H_{22}F_3N_3O_2$ requires 417; found 418 $[M+H]^+$.

117

Example 20

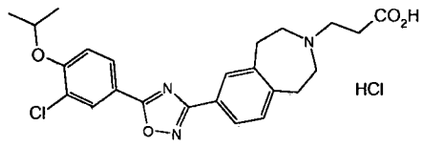
7-{5-[2-(Trifluoromethyl)-4-biphenylyl]-1,2,4-oxadiazol-3-yl}-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride



1,1-Dimethylethyl-7-{5-[2-(trifluoromethyl)-4-biphenylyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (Preparation 45) (440 mg, 0.82 mmol) was dissolved in 4M HCl in dioxane (3 ml) and the solution stirred for 2 h. The title compound was filtered off as a white solid (376 mg, 0.82 mmol). δH (d_6DMSO, 400 MHz): 9.27 (2H, brs), 8.53 (1H, d), 8.51 (1H, dd), 8.01 (1H, d), 7.97 (1H, dd), 7.74 (1H, d), 7.54-7.50 (3H, m), 7.47 (1H, d), 7.43-7.39 (2H, m), 3.28-3.20 (8H, m). MS (ES): $C_{25}H_{20}F_3N_3O$ requires 435; found 436 $[M+H]^+$.

Example 21

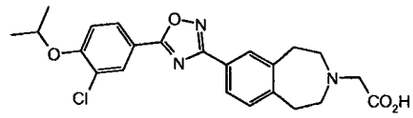
3-[7-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]propanoic acid



A mixture of 7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (Example 17) (200 mg, 0.52 mmol), 1,1-dimethylethyl 2-propenoate (151 µL, 1.04 mmol) and diisopropylethylamine (453 µL, 2.60 mmol) in methanol (5 ml) was heated in the microwave at 90 °C for 30 minutes before the solvent was removed in vacuo. The residue was dissolved in 4M HCl (2 ml) in dioxane and the mixture stirred at room temperature for 5 h. The solvent was removed in vacuo and the residue purified by MDAP. To the product containing fractions was added 2M HCl and the solution concentrated in vacuo to give the title compound as a white solid (116 mg, 0.24 mmol). δH (d_6DMSO, 400 MHz): 12.73 (1H, br.s), 10.76 (1H, br.s), 8.19 (1H, d), 8.11 (1H, dd), 7.98 (1H, d), 7.93 (1H, dd), 7.46 (1H, d), 7.45 (1H, d), 4.89 (1H, septet), 3.76-3.64 (2H, m), 3.44-3.31 (4H, hidden under H_2O peak), 3.25-3.03 (4H, m), 2.89 (2H, t), 1.37 (6H, d). MS (ES): $C_{24}H_{26}{}^{35}ClN_3O_4$ requires 455; found 456 $[M+H]^+$.

Example 22

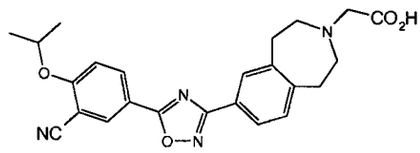
[7-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]acetic acid



A solution of ethyl [7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]acetate (Preparation 46) (77 mg, 0.164 mmol) in methanol (30 ml) was stirred at room temp and sodium hydroxide (3 ml, 6.00 mmol) added. The reaction mixture was stirred at room temperature overnight. The solvent was removed *in vacuo*, the solid was triturated with methanol (~5ml) and the resultant solid filtered off and dried. The solid was suspended in methanol (~30ml) and acetic acid added to take the pH of the solution to 5-6, the solvent was removed *in vacuo*. The resultant residue was dissolved in DCM (~30ml) and water (~30ml) and the layers partitioned. The aqueous was re-extracted with DCM (~20ml) and the combined organics were passed through a phase separation cartridge and the solvent reduced *in vacuo*. The resultant residue was dried in a drying pistol at 60°C to yield the title compound (22 mg, 0.047 mmol, 29 % yield) as an off white solid. δH (d_6DMSO, 400 MHz): 8.19 (1H, s), 8.11 (1H, d), 7.82-7.90 (2H, m), 7.44 (1H, d), 7.36 (1H, d), 4.89 (1H, sept), 3.34 (2H, s), 3.07-2.98 (4H, m), 2.91-2.86 (4H, m), 1.37 (6H, d. MS (ES^+): $C_{23}H_{24}{}^{35}ClN_3O_4$ requires 441; found 442 $[M+H]^+$.

Example 23

[7-(5-{3-Cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl]acetic acid



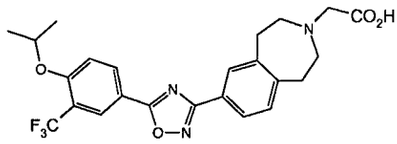
A mixture of ethyl [7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl]acetate (Preparation 47) (43 mg, 0.09 mmol), aqueous sodium hydroxide (2M, 430 µL, 0.86 mmol) and ethanol (4.3 ml) was heated at 40 °C for 1 h. The reaction mixture was cooled to room temperature and concentrated. The residue was taken up in water, which was then acidified to pH 6 with acetic acid. The aqueous phase was extracted with EtOAc (2 x 20 ml) and the combined organic fractions concentrated to give a white solid, which was then triturated with EtOAc to give the title compound as a white solid (36 mg, 0.08 mmol).

119

δH (d_6DMSO, 400 MHz): 8.50 (1H, d), 8.41 (1H, dd), 7.85-7.80 (2H, m), 7.55 (1H, d), 7.32 (1H, d), 4.98 (1H, septet), 3.00-2.91 (6H, m), 2.75-2.66 (4H, m), 1.39 (6H, d); MS (ES-): $C_{24}H_{24}N_4O_4$ requires 432; found 431 [M-H$^+$].

Example 24

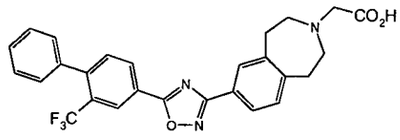
(7-{5-[4-[(1-Methylethyl)oxy]-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl)acetic acid



A mixture of ethyl (7-{5-[4-[(1-methylethyl)oxy]-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl)acetate (Preparation 48) (59 mg, 0.12 mmol), aqueous sodium hydroxide (2M, 590 µL, 1.18 mmol) and ethanol (6 ml) was heated at 40 °C for 1 hr. The reaction mixture was cooled to room temperature and concentrated. The residue was taken up in water, which was then acidified to pH 6 with acetic acid. The aqueous phase was extracted with EtOAc (2 x 20 ml) before the combined organic fractions were concentrated and the residue was triturated with EtOAc and the title compound was filtered off and dried in a vacuum oven to give a white solid (36 mg, 0.08 mmol). δH (d_6DMSO, 400 MHz): 8.41 (1H, dd), 8.30 (1H, d), 7.88-7.82 (2H, m), 7.58 (1H, d), 7.35 (1H, d), 4.98 (1H, septet), 3.25 (2H, s), 3.06-2.96 (4H, m), 2.89-2.81 (4H, m), 1.36 (6H, d); MS (ES-): $C_{24}H_{24}F_3N_3O_4$ requires 475; found 474 [M-H$^+$].

Example 25

(7-{5-[2-(Trifluoromethyl)-4-biphenylyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl)acetic acid



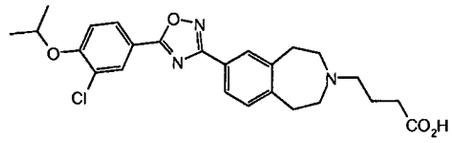
A mixture of ethyl (7-{5-[2-(trifluoromethyl)-4-biphenylyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3*H*-3-benzazepin-3-yl)acetate (Preparation 49) (22 mg, 0.04 mmol), aqueous sodium hydroxide (2M, 220 µL, 0.44 mmol) and ethanol (2.2 ml) was heated at 40 °C for 1 h. The reaction mixture was cooled to room temperature and concentrated. The residue was taken up in water, which was then acidified to pH 6 with acetic acid. The aqueous phase was extracted with EtOAc (2 x 20 ml) before the

120

combined organic fractions were concentrated and the residue was triturated with EtOAc and the title compound was filtered off and dried in a vacuum oven to give a white solid (13 mg, 0.03 mmol). δH (d_6DMSO, 400 MHz): 8.52 (1H, d), 8.50 (1H, dd), 7.92-7.86 (2H, m), 7.73 (1H, d), 7.54-7.49 (3H, m), 7.44-7.35 (3H, m), 3.18 (2H, s), 3.05-2.96 (4H, m), 2.85-2.79 (4H, m); MS (ES-) : $C_{27}H_{22}F_3N_3O_3$ requires 493; found 492 [M-H$^+$].

Example 26

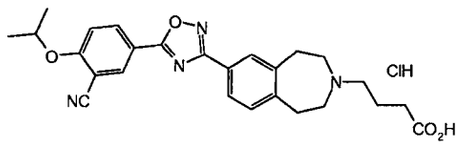
4-[7-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid



A solution of ethyl 4-[7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoate (Preparation 50) (100 mg, 0.201 mmol) in ethanol (6 ml) was stirred at room temp and sodium hydroxide (1.5 ml, 3.00 mmol) added. The reaction mixture was stirred at room temperature for 90 mins and was then acidified with acetic acid to pH 5, and the mixture concentrated *in vacuo*. The resultant residue was dissolved in EtOAc (~30ml) and water (~30ml) and the layers partitioned, the aqueous was re-extracted with EtOAc (~20ml) and the combined organics were passed through a phase separation cartridge and the solvent reduced *in vacuo*. The residue was purified by trituration with methanol, the solid filtered and dried on the sinter to yield the title compound (30 mg, 0.061 mmol, 30 % yield). δH (d_6DMSO, 400 MHz): 8.19 (1H, s), 8.11 (1H, d), 7.79-7.90 (2H, m), 7.44 (1H, d), 7.34 (1H, d), 4.89 (1H, sept), 3.46-3.24 (2H, hidden under H_2O peak), 3.01-2.93 (4H, m), 2.68-2.59 (4H, m), 2.28 (2H, t), 1.70 (2H, quintet) 1.37 (6H, d). MS (ES): $C_{25}H_{28}{}^{35}ClN_3O_4$ requires 469; found 470 [M+H]$^+$.

Example 27

4-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid hydrochloride

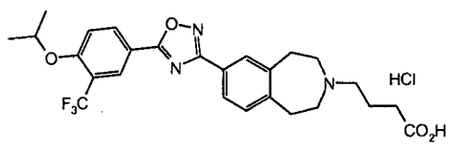


121

A solution of ethyl 4-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoate (Preparation 51) (218 mg, 0.446 mmol) in ethanol (6 ml) was stirred at room temp and sodium hydroxide (2 ml, 4.00 mmol) added. The reaction mixture was stirred at room temperature for 90 minutes and was then acidified with acetic acid to pH 5, and the mixture concentrated *in vacuo*. The resultant residue was dissolved in EtOAc (~30ml) and water (~30ml) and the layers partitioned, the aqueous was re-extracted with EtOAc (~20ml) and the combined organics were passed through a phase separation cartridge and the solvent reduced *in vacuo*. The residue was purified by addition of 10 drops of 2M HCl in ether, followed by trituration with ether, the solid filtered and dried on the sinter and then under vacuum at 60°C to yield the title compound (68 mg, 0.130 mmol, 29 % yield). δH (d_6DMSO, 400 MHz): 8.51 (1H, s), 8.40 (1H, d), 7.97 (1H, s), 7.93 (1H, d), 7.56 (1H, d), 7.47 (1H, d), 4.99 (1H, sept), 3.07-3.80 (10H, m), 2.35 (2H, t), 1.92-2.02 (2H, m), 1.39 (6H, d); MS (ES): $C_{26}H_{28}N_4O_4$ requires 460; found 461 $[M+H]^+$.

Example 28

4-(7-{5-[4-[(1-Methylethyl)oxy]-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)butanoic acid hydrochloride



A solution of ethyl 4-(7-{5-[4-[(1-methylethyl)oxy]-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)butanoate (Preparation 52) (181 mg, 0.341 mmol) in ethanol (6 ml) was stirred at room temp and sodium hydroxide (2 ml, 4.00 mmol) added. The reaction mixture was stirred at room temperature for 90 minutes. The reaction mixture was acidified with acetic acid to pH 5, and the mixture concentrated *in vacuo*. The resultant residue was dissolved in ethyl acetate (~30ml) and water (~30ml) and the layers partitioned, the aqueous phase was re-extracted with ethyl acetate (~20ml) and the combined organics were passed through a phase separation cartridge and the solvent reduced *in vacuo*.

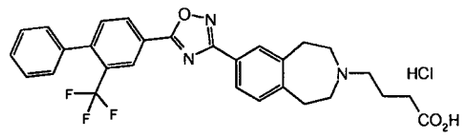
The residue was purified by addition of 10 drops of 2M HCl in ether, followed by trituration with ether, the solid filtered and dried on the sinter to yield the title compound (119 mg, 0.21 mmol, 62 % yield). δH (d_6DMSO, 400 MHz): 8.40 (1H, d), 8.32 (1H, s), 7.97 (1H, s), 7.94 (1H, d), 7.59 (1H, d), 7.45 (1H, d), 4.98 (1H, sept),

122

3.09-3.82 (10H, m), 2.35 (2H, t), 1.90-2.01 (2H, m), 1.36 (6H, d); MS (ES) : $C_{26}H_{28}F_3N_3O_4$ requires 503; found 504 $[M+H]^+$.

Example 29

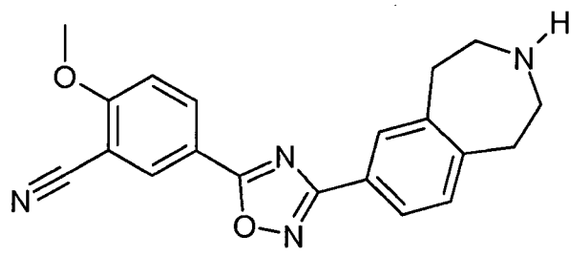
4-(7-{5-[2-(Trifluoromethyl)-4-biphenylyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)butanoic acid hydrochloride



A solution of ethyl 4-(7-{5-[4-{(1E)-1-[(1Z)-1-propen-1-yl]-1,3-butadien-1-yl}-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)butanoate (Preparation 53) (277 mg, 0.504 mmol) in ethanol (6 ml) was stirred at room temperature and sodium hydroxide (2 ml, 4.00 mmol) added. The reaction mixture was stirred at room temperature for 90 minutes and was then acidified with acetic acid to pH 5, and the mixture concentrated *in vacuo*. The resultant residue was dissolved in EtOAc (~30ml) and water (~30ml) and the layers partitioned, the aqueous was re-extracted with EtOAc (~20ml) and the combined organics were passed through a phase separation cartridge and the solvent reduced in-vacuo. The residue was purified by addition of 10 drops of 2M HCl in ether, followed by trituration with ether, the solid filtered and dried on the sinter and overnight under vacuum at 60°C to yield the title compound (120 mg, 0.20 mmol, 41 % yield). δH (d_6DMSO, 400 MHz): 8.53 (1H, s), 8.50 (1H, d), 8.01 (1H, s), 7.97 (1H, d), 7.75 (1H, d), 7.37-7.56 (6H, m), 3.14-3.41 (8H, m), 3.07 (2H, br s), 2.34 (2H, t), 1.87-1.99 (2H, m). MS (ES) : $C_{29}H_{26}F_4N_3O_3$ requires 521; found 522 $[M+H]^+$.

Example 30

2-(Methyloxy)-5-[3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1,2,4-oxadiazol-5-yl]benzonitrile hydrochloride



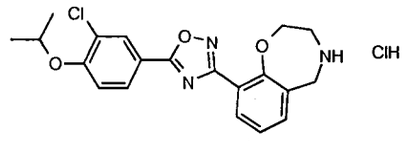
A solution of 1,1-dimethylethyl 7-{5-[3-cyano-4-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (Preparation 54) (280 mg,

123

0.627 mmol) in hydrochloric acid 4M solution in dioxane (5 ml, 20.00 mmol) and 1,4-dioxane (5 ml) was stirred at room temperature overnight. The reaction mixture was filtered and washed with dioxane (~5ml), and the solid dried under vacuum to yield the title compound (177 mg, 0.393 mmol, 62.7 % yield) as an off white solid. δH (d_6DMSO, 400 MHz): 8.99-9.31 (2H, m), 8.53 (1H, s), 8.46 (1H, d), 7.96 (1H, s), 7.93 (1H, d), 7.54 (1H, d), 7.46 (1H, d), 4.07 (3H, s), 3.09-3.31 (7H, m); MS (ES): $C_{20}H_{18}N_4O_2$ requires 346; found 347 $[M+H]^+$.

Example 31

9-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrochloride

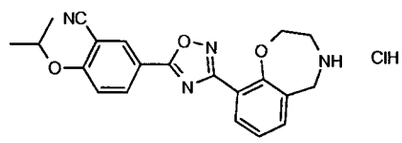


1,1-Dimethylethyl 9-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (Preparation 66) (320mg, 0.658 mmol) was dissolved in 1,4-dioxane (1ml) and treated with HCl (2 ml, 8.00 mmol) in 1,4-dioxane. The reaction mixture was left at RT for 1hr, evaporated and then triturated with ether to give the title compound (180mg) as a white solid. MS (ES): $C_{20}H_{20}{}^{35}ClN_3O_3$ requires 385; found 386 $[M+H]^+$.

The following compound was prepared by a similar method.

Example 32

2-[(1-Methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1,4-benzoxazepin-9-yl)-1,2,4-oxadiazol-5-yl]benzonitrile hydrochloride

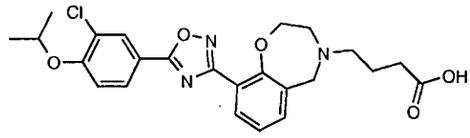


Prepared in a similar way to Example 31 from Preparation 67. MS (ES): $C_{21}H_{20}N_4O_3$ requires 376; found 377 $[M+H]^+$.

Example 33

124

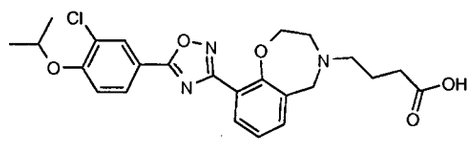
4-[9-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]butanoic acid



A solution of ethyl 4-[9-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]butanoate (Preparation 68) (130 mg, 0.260 mmol) in ethanol was treated with sodium hydroxide (10.4mg in 1ml, 0.260 mmol). The reaction mixture was left standing at RT for 1hour then evaporated. The resulting crude was partitioned between EtOAc/water, acidified with acetic acid, separated and the organivs dried over magnesium sulphate and evaporated. The title compound (61mg) was obtained by trituration with ether as a white solid. δH (d_6DMSO, 400 MHz): 1.36 (6H, d), 1.69 (2H, m), 2.23 (2H, t), 2.43 (2H, t), 3.05 (2H, m), 3.86 (2H, s), 4.07 (2H, m), 4.88 (1H, m), 7.20 (1H, t), 7.43-7.49 (2H, m), 7.78 (1H, dd), 8.09 (1H, dd), 8.17 (1H, d), 12.10 (1H, br. s); MS (ES-): $C_{24}H_{26}{}^{35}ClN_3O_5$ requires 471; found 470 [M-H$^+$].

<u>Example 33 Alternative preparation</u>

4-[9-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]butanoic acid



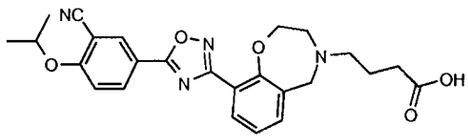
A solution of ethyl 4-[9-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]butanoate (Preparation 68) (61.7 g, 123 mmol) in ethanol (600 ml) was treated with 2M sodium hydroxide (123 ml, 247 mmol) and the mixture stirred at room temperature overnight. The solvent was evaporated and the residue dissolved in water (1 litre). The aqueous solution was cooled in ice/water and treated slowly with glacial acetic acid (28.3 ml, 494 mmol). The resulting gum was stirred vigorously until a filterable solid was obtained which was then collected by filtration and washed with more water (2x 500 ml). After sucking the pad dry the material was dissolved in a 95:5 mixture of dichloromethane / methanol and dried (sodium sulphate). The solvent was removed by evaporation and the resulting solid was triturated under diethyl ether (200 ml), collected by filtration,

washed with diethyl ether and dried to give the title compound as a colourless solid (54g).

MS (ES) $C_{24}H_{26}{}^{35}ClN_3O_5$ requires 471; found 472 $[M+H]^+$.

Example 34

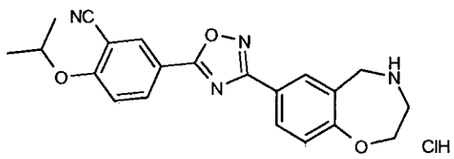
4-[9-(5-{3-Cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]butanoic acid



Prepared in a similar way to Example 33 from Preparation 69. δH (d_6DMSO, 400 MHz): 1.38 (6H, d), 1.69 (2H, m), 2.23 (2H, t), 2.43 (2H, t), 3.05 (2H, m), 3.86 (2H, s), 4.07 (2H, m), 4.98 (1H, m), 7.20 (1H, t), 7.47 (1H, dd), 7.54 (1H, d), 7.77 (1H, dd), 8.38 (1H, dd), 8.49 (1H, d), 12.10 (1H, br. s); MS (ES): $C_{25}H_{26}N_4O_5$ requires 462; found 463 $[M+H]^+$.

Example 35

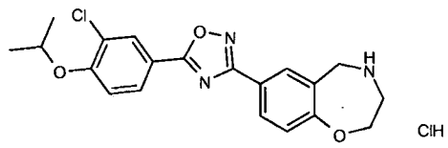
2-[(1-Methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1,2,4-oxadiazol-5-yl]benzonitrile hydrochloride



1,1-Dimethylethyl 7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (Preparation 76) (0.410 g, 0.860 mmol) was dissolved in 1,4-dioxane (1 ml). Added HCl (1 ml, 4.00 mmol)in dioxane (4M) and stirred at R.T. for 2 hours. Added ether, filtered and dried in the oven under vacuum at R.T. to give 0.26g of white solid. 50mg was purified by MDAP to give the title compound (13mg) as a cream solid. δH (MeOD, 400 MHz): 1.44 (6H, d), 3.63 (2H, m), 4.33 (2H, m), 4.52 (2H, s), 4.92 (1H, m), 7.30 (1H, d), 7.43 (1H, d), 8.15 (1H, dd), 8.21 (1H, d), 8.38 (1H, dd), 8.45 (1H, d) ; MS (ES): $C_{21}H_{20}N_4O_3$ requires 376; found 377 $[M+H]^+$.

Example 36

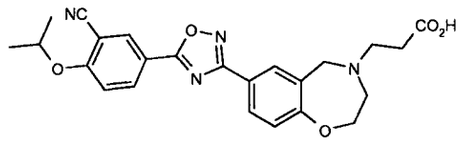
7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrochloride



Prepared by a similar method to Example 35 from Preparation 77. δH (d_6DMSO, 400 MHz): 1.35 (6H, d), 3.51 (3H, m), 4.31 (2H, m), 4.82 (2H, s), 4.85 (1H, m), 7.23 (1H, d), 7.45 (1H, d), 7.97-8.12 (2H, m), 8.18 (2H, m) ; MS (ES): $C_{20}H_{20}{}^{35}ClN_3O_3$ requires 385; found 386 $[M+H]^+$.

Example 37

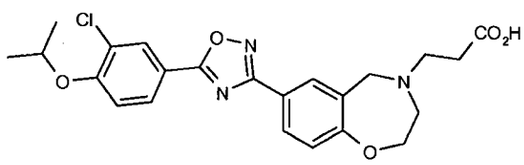
3-[7-(5-{3-Cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]propanoic acid



Ethyl 3-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propanoate (Preparation 78) (0.092 g, 0.193 mmol) was dissolved in Ethanol (2 ml). Then 2N NaOH (1 ml, 2.000 mmol) was added and the reaction mixture left standing at RT for 2 hours. Ethanol was removed by evaporation and the resulting residue dissolved in EtOAc and water, acidified with acetic acid and the layers separated. Solid separated from the aqueous phase and was filtered off solid and dried under vacuum overnight at 50°C to give the title compound (8mg) as a white solid. δH (d_6DMSO, 400 MHz): 1.37 (6H, d), 2.38 (2H, t), 2.67 (2H, m), 3.03 (2H, m), 3.89 (2H, s), 4.07 (2H, m), 4.97 (1H, m), 7.14 (1H, d), 7.54 (1H, d), 7.89 (1H, dd), 7.98 (1H, d), 8.39 (1H, dd), 8.51 (1H, d); MS (ES): $C_{24}H_{24}N_4O_5$ requires 448; found 449 $[M+H]^+$.

Example 38

3-[7-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]propanoic acid

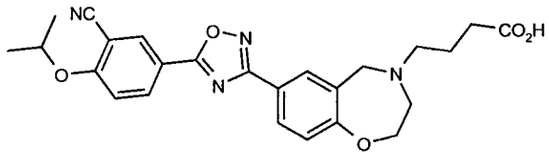


Prepared by a similar method to Example 37 from Preparation 79. δH (d_6DMSO, 400 MHz): 1.36 (6H, d), 2.43 (2H, t), 2.70 (2H, m), 3.04 (2H, m), 3.91 (2H, s), 4.07 (2H,

m), 4.87 (1H, m), 7.14 (1H, d), 7.43 (1H, d), 7.89 (1H, dd), 7.99 (1H, d), 8.09(1H, dd), 8.18 (1H, d) ; MS (ES): $C_{23}H_{24}{}^{35}ClN_3O_5$ requires 457; found 458 $[M+H]^+$.

Example 39

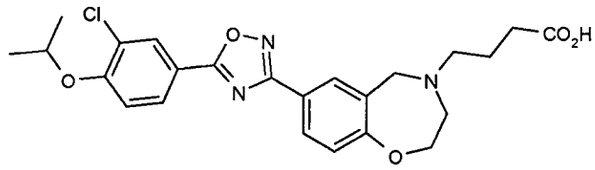
4-[7-(5-{3-Cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]butanoic acid



Ethyl 4-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]butanoate (Preparation 80) (0.084 g, 0.171 mmol) was dissolved in Ethanol (2 ml). Then 2N NaOH (1 ml, 2.000 mmol) was added and the reaction left standing at RT for 3 hours. Ethanol was removed by evaporation and the resulting residue dissolved in EtOAc and water, acidified with acetic acid and the phases separated. The organic phase was dried ($MgSO_4$), evaporated and triturated with ether. Drying under vacuum overnight at 50°C yielded the title compound (22mg) as a white solid. δH (d_6DMSO, 400 MHz): 1.37 (6H, d), 1.66 (2H, t), 2.22 (2H, t), 2.45 (2H, m), 3.01 (2H, m), 3.82 (2H, s), 4.07 (2H, m), 4.95 (1H, m), 7.14 (1H, d), 7.54 (1H, d), 7.89 (1H, dd), 7.96 (1H, d), 8.38(1H, dd), 8.50 (1H, d); MS (ES): $C_{25}H_{26}N_4O_5$ requires 462; found 463 $[M+H]^+$.

Example 40

4-[7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]butanoic acid

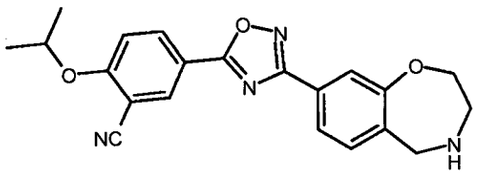


Prepared by hydrolysis of the ester, Preparation 81, using the method described for Example 37. δH (d_6DMSO, 400 MHz): 1.36 (6H, d), 1.68 (2H, t), 2.23 (2H, t), 2.45 (2H, m), 3.01 (2H, m), 3.87 (2H, s), 4.07 (2H, m), 4.87 (1H, m), 7.13 (1H, d), 7.43 (1H, d), 7.89 (1H, dd), 7.95 (1H, d), 8.09 (1H, dd), 8.52 (1H, d); MS (ES): $C_{24}H_{26}{}^{35}ClN_3O_5$ requires 471; found 472 $[M+H]^+$.

128

Example 41

2-[(1-Methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1,4-benzoxazepin-8-yl)-1,2,4-oxadiazol-5-yl]benzonitrile

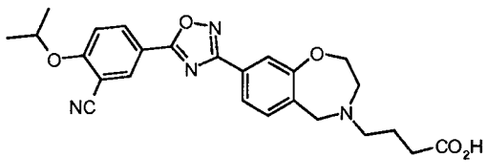


ClH

Prepared from Preparation 82 using a similar procedure to Example 35. MS (ES): $C_{21}H_{20}N_4O_3$ requires 376; found 377 $[M+H]^+$.

Example 42

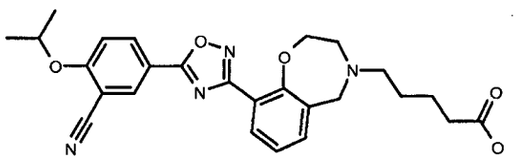
4-[8-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]butanoic acid



Prepared from Preparation 83 using the method described in Example 15. δH (d_6DMSO, 400 MHz): 1.38 (6H, d), 1.69 (2H, m), 2.21 (2H, t), 2.42 (2H, t), 3.02 (2H, m), 3.84 (2H, s), 4.06 (2H, m), 4.97 (1H, m), 7.44 (1H, d), 7.54 (1H, d), 7.61 (1H, d), 7.71 (1H, dd), 8.39 (1H, dd), 8.50 (1H, d), 12.10 (1H, br.s); MS (ES): $C_{25}H_{26}N_4O_5$ requires 462; found 463 $[M+H]^+$.

Example 43

5-[9-(5-{3-Cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]pentanoic acid



2M sodium hydroxide (0.347 mL, 0.694 mmol) was added to a stirred solution of ethyl 5-[9-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]pentanoate (Preparation 93) (70 mg, 0.139 mmol)

129

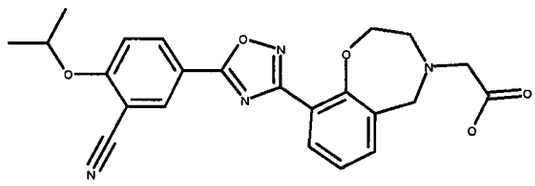
in ethanol (5 mL) and the mixture was heated to 60°C overnight. The reaction mixture was allowed to cool to room temperature and the solvent evaporated. The residue was diluted with water, acidified with 2M hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with water, dried and evaporated to give the product as an off white solid (20mg).

δH (400 MHz, $CDCl_3$). 1.47 (6h, d), 1.59-1.70 (4H, m), 2.3 (2H, t), 2.61 (2H, t), 3.25-3.29 (2H, m), 4.05 (2H, s), 4.24-4.28 (2H, m), 4.79 (1H, m), 7.12 (1H, d), 7.20 (1H, dd), 7.39 (1H, d), 7.95 (1H, d), 8.30 (1H, dd), 8.43 (1H, s).

MS (ES) $C_{26}H_{28}N_4O_5$ requires 476 Found 477 $[M+H]^+$.

Example 44

[9-(5-{3-Cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]acetic acid



2M sodium hydroxide (0.54 ml, 1.08 mmol) was added to a stirred solution of ethyl [9-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]acetate (Preparation 86) (100 mg, 0.216 mmol) in ethanol (10 ml) and the mixture was stirred at room temperature for 2h. The solvent was evaporated before diluting with water, acidifying with 2M hydrochloric acid and extracting with ethyl acetate. The organic extract was washed with water, dried and evaporated to give the product as an off white solid (30mg).

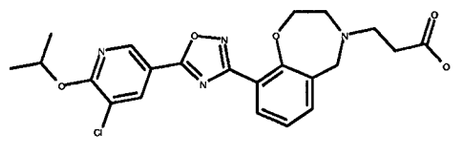
δH (400 MHz, D_6-DMSO). 1.39 (6H, d), 3.88-4.02 (2H,m), 4.09-4.13 (2H, m), 4.98 (1H, m), 7.43 (1H, d), 7.56 (1H, d), 7.82 (1H, d), 8.39 (1H, d), 8.50 (1H, s). Missing peaks obscured by water and residual solvent.

MS (ES) $C_{23}H_{22}N_4O_5$ requires 434 Found 435 $[M+H]^+$.

Example 45

3-[9-(5-{5-Chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propanoic acid

130



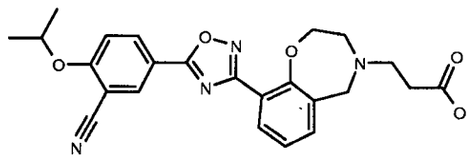
Ethyl 3-[9-(5-{5-chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propanoate (Preparation 91) (28 mg, 0.058 mmol) was dissolved in ethanol (5 ml). 2M sodium hydroxide (0.144 ml, 0.288 mmol) was added and the reaction mixture stirred at 60°C for 4 hours. The solvent was evaporated and the reaction mixture diluted with water, neutralised with 2M hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with water, dried and evaporated to give the product as a white solid (26mg).

δH (400 MHz, $CDCl_3$). 1.46 (6H, d), 2.54 (2H, br t), 2.91 (2H, br t), 3.36 (2H, m), 4.12 (2H, s), 4.28 (2H , br m), 5.48 (1H, m), 7.21-7.29 (1H, m), 7.39 (1H, d), 8.00 (1H, d), 8.38 (1H, s), 8.88 (1H, s).

MS (ES) $C_{22}H_{23}{}^{35}ClN_4O_5$ requires 458 Found 459 $[M+H]^+$.

Example 46

3-[9-(5-{3-Cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propanoic acid



Ethyl 3-[9-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propanoate (Preparation 92) (40 mg, 0.084 mmol) was dissolved in ethanol (5 ml). 2M sodium hydroxide (0.210 ml, 0.420 mmol) was added and the reaction mixture stirred at 60°C for 4 hours. The solvent was evaporated, then the reaction mixture was diluted with water, neutralised with 2M hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with water, dried and evaporated to give the product as a colourless solid (16mg).

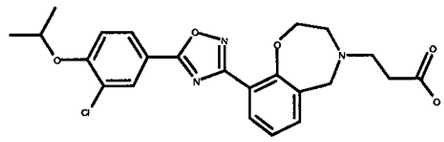
δH (400 MHz, $CDCl_3$). 1.47 (6H, d), 2.56 (2H, br t), 2.92 (2H, br t), 3.34-3.39 (2H, m), 4.13 (2H, br s), 4.25-4.31 (2H, m), 4.79 (1H, m), 7.13 (1H, d), 7.20-7.28 (1H, m), 7.40 (1H, d), 8.00 (1H, d), 8.33 (1H, d), 8.42 (1H, s).

MS (ES) $C_{22}H_{24}N_4O_5$ requires 448 Found 449 $[M+H]^+$.

Example 47

131

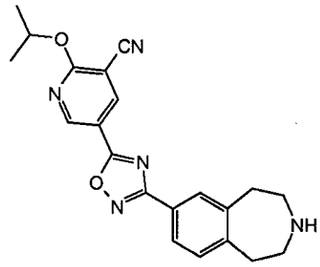
3-[9-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propanoic acid



Ethyl 3-[9-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propanoate (Preparation 88) (60 mg, 0.123 mmol) was dissolved in ethanol (5 ml). 2M sodium hydroxide (0.309 ml, 0.617 mmol) was added and the reaction mixture was stirred at 60°C for 4h. The solvent was evaporated then the reaction mixture was diluted with water and neutralised with 2M hydrochloric acid and extracted with ethyl acetate. The organic phase was washed with water, dried and evaporated to give the product as a colourless solid (27mg).
δH (400 MHz, D_6-DMSO). 1.36 (6H,d), 2.42 (2H, br t), 2.65-2.70 (2H, m), 3.90 (2H, s), 4.04-4.09 (2H, m), 4.88 (1H, m), 7.21 (1H, dd), 7.44 (1H, d), 7.51 (1H, d), 7,79 (1H, d), 8.09 (1H, d), 8.17 (1H,s).
MS (ES) $C_{23}H_{24}{}^{35}ClN_3O_5$ requires 457 Found 458 $[M+H]^+$.

Example 48

2-[(1-Methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1,2,4-oxadiazol-5-yl]-3-pyridinecarbonitrile formate



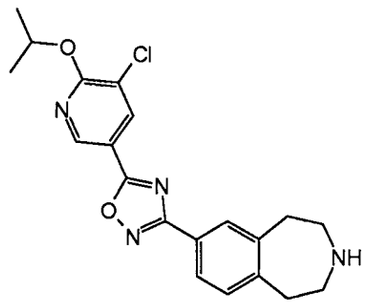
1,1-Dimethylethyl 7-(5-{5-cyano-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (Preparation 95) (224 mg, 0.471 mmol) in dichloromethane (1 ml) was treated with 4M HCl in dioxan (5 ml, 20.0 mmol). The colourless solution was left at room temperature over the week-end to give a colourless precipitate. The reaction mixture was concentrated, triturated with ether and dried. The crude product was treated with DMSO:MeOH (1:1; 1.9ml), the mixture filtered and the filtrate purified by MDAP. The title compound was obtained as a formate salt (55mgs), δH (400 MHz, d_6DMSO), 1.41 (6H, d), 3.07-3.20 (4H,m),

132

5.51 (1H, m), 7.42 (1H, d), 7.88 (1H dd), 7.91 (1H, d), 8.24 (1H, s), 8.98 (1H, d) and 9.20 (1H, d) ; MS (ES) $C_{21}H_{21}N_5O_2$ requires 375; found 376$[M+H]^+$.

Example 49

7-(5-{5-Chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride



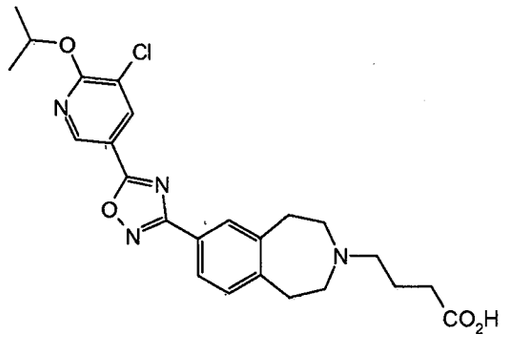
1,1-Dimethylethyl 7-(5-{5-chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (Preparation 96) (305 mg, 0.629 mmol) in dichloromethane (2 mL) at room temperature was treated with trifluoroacetic acid (1 ml, 12.98 mmol) and the mixture stirred for 1 hr. The reaction mixture was concentrated and the residue partitioned between 2M NaOH and ethyl acetate. The ethyl acetate extract was washed with brine, dried and concentrated to a colourless gum which slowly crystallized, to give the title compound free base (229mgs).

A portion of the free base (37mg) was dissolved in methanol (0.5ml) and treated with excess HCl in methanol (1.25M; 0.4ml). The solution was evaporated to give the title compound as a colourless solid (42mgs).

δH (400 MHz, d_6DMSO), 1.39 (6H, d), 3.21 (8H, d), 5.45 (1H, m), 7.45 (1H, d), 7.91 (1H, dd), 7.95 (1H, d), 8.55 (1H, d), 8.92 (1H, d) and 9.33 (2H, br s) ; MS (ES) $C_{20}H_{21}{}^{35}ClN_4O_2$ requires 384; found 385 $[M+H]^+$.

Example 50

4-[7-(5-{5-Chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid



A suspension of ethyl 4-[7-(5-{5-chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoate (Preparation 97) (185 mg, 0.371 mmol) in ethanol (3 ml), was treated with 2M sodium hydroxide (0.556 ml, 1.11 mmol) at room temperature overnight to give a colourless precipitate. A further 1-2mls of ethanol was added and the temperature was raised to 50°C to complete the reaction. Acetic acid (0.07 ml, 1.22mmol) was added to the solution and the mixture concentrated. The resultant oily residue was treated with water (*ca* 3 ml) then stirred at room temperature for 1-2hr and filtered. The solid was washed with water, then dissolved in methanol and the solvent evaporated. The resultant solid was dried overnight *in vacuo* at *ca* 60°C to give the title compound (153mgs).

δH (400 MHz, d_6DMSO), 1.39 (6H, d), 1.69 (2H, m) 2.26 (2H, t), 2.47 (2H, t), 2.61 (4H, br s), 2.95 (4H, br m), 5.45 (1H, m), 7.34 (1H, d), 7.80-7.85 (2H, m), 8.53 (1H, d) and 8.90 (1H, d) ; MS (ES) $C_{24}H_{27}{}^{35}ClN_4O_4$ requires 470; found 471 $[M+H]^+$.

Membrane preparation for S1P1 GTPγS assay

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 were homogenised within a glass Waring blender for 2 bursts of 15secs in 200mls of buffer (50mM HEPES, 1mM leupeptin, 25μg/ml bacitracin, 1mM EDTA, 1mM PMSF, 2μM 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 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

134

volume, (usually x4 the volume of the original cell pellet), aliquoted and stored frozen at –80°C.

Alternative Membrane preparation for S1P1 GTPγS 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, 25μg/ml bacitracin, 1mM EDTA, 1mM PMSF, 2μM 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 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

S1P1 GTPγS assay

Human S1P1 rat hepatoma membranes (1.5μg/well) were adhered to a wheatgerm agglutinin (WGA)-coated scintillation proximity assay (SPA) beads (0.125mg/well) in assay buffer (HEPES 20mM, $MgCl_2$ 10mM, NaCl 100mM and pH adjusted to 7.4 using KOH 5M, GDP 10μM FAC (final assay concentration) and saponin 90μg/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 (5μl/well), containing 0.1μl of the compound. 5μl/well [^{35}S]-GTPγS (0.5nM final radioligand conc) made up in assay buffer was then added to agonist plates. The final assay cocktail (10.1μl) 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 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.

Alternative method for S1P1 GTPγS assay

135

S_1P_1 expressing RH7777 membranes (1.5μg/well) membranes (1.5μg/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, $MgCl_2$ 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 dispensed into white Greiner polypropylene LV 384-well plates (5μl/well), containing 0.1μl of compound. 5μl/well [^{35}S]-GTPγS (0.5nM for S_1P_1 or 0.3nM for S_1P_3 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.

Exemplified compounds of the invention had a pEC50 > 5, many had a pEC50 >7. Examples 6, 7, 8, 12, 18, 19, 21 to 29, 31 to 35, 37, 39, 41, 43, 47, 48 and 50 had a pEC50 >7. Examples 7, 21, 23, 24 and 26 to 28 had a pEC50 ≥8.

S1P3 GTPγS assay

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, $MgCl_2$ 3mM, NaCl 100mM and pH adjusted to 7.4 using KOH 5M), GDP 10μM FAC and saponin 90μg/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 (5μl/well), containing 0.1μl of the compound. 5μl/well [^{35}S]-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 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.

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.

136

Alternative method for S1P3 GTPγS assay

S_1P_3 expressing RBL membranes (1.5μg/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, $MgCl_2$ 10mM, NaCl 100mM and pH adjusted to 7.4 using KOH 5M). GDP 10μM FAC and saponin 90μg/ml FAC were also added

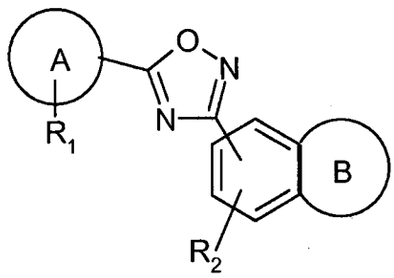
After 30 minutes precoupling on ice, the bead and membrane suspension was dispensed into white Greiner polypropylene LV 384-well plates (5μl/well), containing 0.1μl of compound. 5μl/well [^{35}S]-GTPγS (0.5nM for S_1P_1 or 0.3nM for S_1P_3 final radioligand concentration) made in assay buffer was then added to the plates. The final assay cocktail (10.1μl) was then sealed, spun on a centrifuge, then read immediately on a Viewlux instrument.

Exemplified compounds had a pEC50 < 6, many had a pEC50 <5. Examples 1 to 5, 8 to 14, 16, to 22, 26, 30 to 34, 36, 37, 39 to 41, 43 to 50 had a pEC50 ≤5.

137

Claims

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



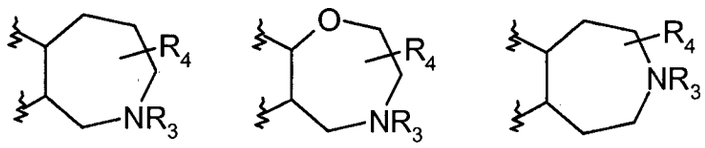
(I)

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

R_1 is up to two substituents independently selected from halogen, $C_{(1-3)}$alkoxy, $C_{(1-3)}$fluoroalkyl, cyano, optionally substituted phenyl, $C_{(1-3)}$fluoroalkoxy, $C_{(1-6)}$alkyl and $C_{(3-6)}$cycloalkyl;

R_2 is hydrogen, halogen or $C_{(1-4)}$alkyl;

B is a 7 membered saturated ring selected from the following:



(a) (b) (c)

R_3 is hydrogen or $(CH_2)_{1-4}CO_2H$;

R_4 is hydrogen or $C_{(1-3)}$alkyl optionally interrupted by oxygen;

2. A compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein:

A is phenyl;

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

R_2 is hydrogen;

B is (a);

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

R_4 is hydrogen.

136

3. A compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein:

A is phenyl or pyridinyl; and/or

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

R_2 is hydrogen; and/or

B is (b); and/or

R_3 is hydrogen or $(CH_2)_{1-4}CO_2H$; and/or

R_4 is hydrogen.

4. A compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein:

A is phenyl or pyridinyl;

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

R_2 is hydrogen;

B is (c);

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

R_4 is hydrogen.

5. A compound according to claim 1 selected from:

7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1H-2-benzazepine

[7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]acetic acid

2-[(1-methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1H-2-benzazepin-7-yl)-1,2,4-oxadiazol-5-yl]benzonitrile

[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]acetic acid

4-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]butanoic acid

129

3-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]propanoic acid

2-[(1-methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1H-3-benzazepin-6-yl)-1,2,4-oxadiazol-5-yl]benzonitrile

6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1H-3-benzazepine

3-[6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]propanoic acid

[6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]acetic acid

6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1H-2-benzazepine

[6-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,3,4,5-tetrahydro-2H-2-benzazepin-2-yl]acetic acid

8-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine

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

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

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

7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1H-3-benzazepine

2-[(1-methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1,2,4-oxadiazol-5-yl]benzonitrile

7-{5-[4-[(1-methylethyl)oxy]-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-2,3,4,5-tetrahydro-1H-3-benzazepine

7-{5-[2-(trifluoromethyl)-4-biphenylyl]-1,2,4-oxadiazol-3-yl}-2,3,4,5-tetrahydro-1H-3-benzazepine

3-[7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]propanoic acid

[7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]acetic acid

[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]acetic acid

(7-{5-[4-[(1-methylethyl)oxy]-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)acetic acid

(7-{5-[2-(trifluoromethyl)-4-biphenylyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)acetic acid

4-[7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

4-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

4-(7-{5-[4-[(1-methylethyl)oxy]-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)butanoic acid

4-(7-{5-[2-(trifluoromethyl)-4-biphenylyl]-1,2,4-oxadiazol-3-yl}-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)butanoic acid

141

2-(Methyloxy)-5-[3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1,2,4-oxadiazol-5-yl]benzonitrile

9-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine

2-[(1-methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1,4-benzoxazepin-9-yl)-1,2,4-oxadiazol-5-yl]benzonitrile

4-[9-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]butanoic acid

4-[9-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]butanoic acid

2-[(1-methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1,2,4-oxadiazol-5-yl]benzonitrile

7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrochloride

3-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propanoic acid

3-[7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propanoic acid

4-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]butanoic acid

4-[7-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]butanoic acid

2-[(1-methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1,4-benzoxazepin-8-yl)-1,2,4-oxadiazol-5-yl]benzonitrile

142

4-[8-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]butanoic acid

5-[9-(5-{3-Cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]pentanoic acid

[9-(5-{3-Cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]acetic acid

3-[9-(5-{5-Chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propanoic acid

3-[9-(5-{3-Cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propanoic acid

3-[9-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]propanoic acid

2-[(1-Methylethyl)oxy]-5-[3-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1,2,4-oxadiazol-5-yl]-3-pyridinecarbonitrile formate

7-(5-{5-Chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride

4-[7-(5-{5-Chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid

and pharmaceutically acceptable salts thereof.

6. A compound according to claim 1, which is
4-[7-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]butanoic acid hydrochloride
or a pharmaceutically acceptable salt thereof.

7. A compound according to claim 1, which is

143

4-[9-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]butanoic acid
or a pharmaceutically acceptable salt thereof.

8. Use of a compound according to any one of claims 1 to 7 for the treatment of conditions or disorders mediated by S1P1 receptors.

9. Use according to claim 8, wherein the condition or disorder is multiple sclerosis, autoimmune diseases, chronic inflammatory disorders, asthma, inflammatory neuropathies, arthritis, transplantation, Crohn's disease, ulcerative colitis, lupus erythematosis, 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. Use according to claim 9, wherein the condition is lupus erythematosis.

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

12. Use according to claim 11, wherein the condition or disorder multiple sclerosis, autoimmune diseases, chronic inflammatory disorders, asthma, inflammatory neuropathies, arthritis, transplantation, Crohn's disease, ulcerative colitis, lupus erythematosis, 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.

13. Use according to claim 12, wherein the condition is lupus erythematosis.

14. A pharmaceutical composition comprising a compound according to any one of claims 1 to 7.

15. 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.

16. A method of treatment according to claim 15, wherein the condition is lupus erythematosis.

DERIVADOS DE OXADIAZOL ACTIVOS SOBRE FOSFATO DE ESFINGOSINA-1

MEMORIA DESCRIPTIVA

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 varios trastornos.

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

de ARNm diferencial, con S1P1-3 siendo ampliamente expresado, S1P4 expresado sobre tejidos linfoide y hematopoyético y S1P5 principalmente en el cerebro y a un menor grado en el bazo. Señalizan mediante diferentes subconjuntos de proteínas G para promover una variedad de respuestas biológicas (Kluk y Hla 2002 Biochem et Biophysica Acta 1582:72, Sanchez y Hla 2004, J Cellular Biochem 92:913).

Los papeles propuestos para su receptor de S1P1 incluyen tráfico de linfocitos, inducción/supresión de citocina y efectos sobre células endoteliales (Rosen y Goetzl 2005 Nat Rev Immunol. 5:560). Los agonistas del receptor de S1P1 se han usado en un número de modelos animales autoinmunes y de trasplante, incluyendo modelos de encefalomielitis autoinmunes experimentales (EAE) de MS, para reducir la severidad 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). Esta actividad se reporta que es mediada por el efecto de agonistas de S1P1 sobre la circulación de linfocitos a través del sistema linfoide. El tratamiento con agonistas de S1P1 da por resultado el secuestro de linfocitos dentro de órganos linfoides secundarios tales como los nodos linfáticos, que inducen una linfopenia periférica reversible en modelos animales (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). Datos publicados sobre agonistas sugieren que el tratamiento con compuesto induce pérdida del receptor de S1P1 de la

superficie celular por 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 de receptor de S1P1 sobre células inmunes lo que contribuye a la reducción del movimiento de células T de los nodos linfáticos de regreso hacia el torrente sanguíneo.

La deleción del gen de S1P1 causa letalidad embrionaria. Experimentos para examinar el papel del receptor de S1P1 en migración y tráfico de linfocitos ha incluido la transferencia adoptiva de células T deficientes en S1P1 marcadas en ratones de tipo silvestre irradiados. Estas células mostraron un egreso reducido de órganos linfoides secundarios (Matloubian et al 2004 Nature 427:355).

A S1P1 también se ha atribuido un papel en la modulación de 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, los agonistas de S1P1 se ha reportado que tienen un efecto sobre nodos linfáticos aislados que pueden estar contribuyendo a un papel en la modulación de trastornos inmunológicos. Los agonistas de S1P1 causaron un cierre de las 'compuertas' estromales endoteliales de senos linfáticos que drenan los nodos linfáticos y previenen el egreso de linfocitos (Wei et al 2005, Nat. Immunology 6:1228).

Se ha mostrado que el compuesto inmunosupresor FTY720 (JP11080026-A) reduce los linfocitos circulantes en animales y el hombre, tiene actividad moduladora de enfermedad en modelos animales de trastornos

inmunológicos y reduce las tasas 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 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 de S1P1, S1P3, S1P4 y S1P5. Estudios clínicos han 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 piensa que la bradicardia se debe a agonismo en el receptor de S1P3, con base en un número de experimentos basados en células y con animales. Estos incluyen el uso de animales knock-out para S1P3 que, a diferencia de los ratones de tipo silvestre, no muestran bradicardia después de la administración de FTY720 y el uso de compuestos selectivos de S1P1. (Hale et al 2004 Bioorganic & Medicinal Chemistry Letters 14:3501, Sanna et al 2004 JBC 279:13839, Koyrakh et al 2005 American J Transplantación 5:529)

Por lo tanto, existe la necesidad de compuestos agonistas de receptor de S1P1 con selectividad sobre S1P3 que se podría esperar que mostraran una tendencia reducida a inducir bradicardia.

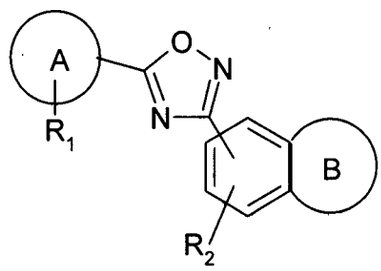
Las siguientes solicitudes de patente describen derivados de oxadiazol como agonistas de S1P1: WO03/105771, WO05/058848, WO06/047195, WO06/100633, WO06/115188, WO06/131336, WO07/024922 y WO07/116866.

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

El documento WO08/064377 describe análogos de benzocicloheptilo que tienen actividad de receptor de S1P1.

Una clase estructuralmente novedosa de compuestos se ha encontrado ahora que provee agonistas del receptor de S1P1.

La presente invención provee compuestos de fórmula (I) o una sal farmacéuticamente aceptable de los mismos:



(I)

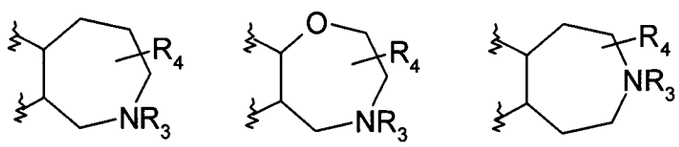
A es fenilo o un anillo de heteroarilo de 5 ó 6 miembros;

R_1 es de hasta dos sustituyentes independientemente seleccionados de halógeno, alcoxi de$C_{(1-3)}$, fluoroalquilo de $C_{(1-3)}$, ciano, fenilo opcionalmente sustituido, fluoroalcoxi de $C_{(1-3)}$, alquilo de $C_{(1-6)}$ y cicloalquilo

de $C_{(3-6)}$;

R_2 es hidrógeno, halógeno o alquilo de $C_{(1-4)}$;

B es un anillo saturado de 7 miembros seleccionado de los siguientes:



(a) (b) (c)

R_3 es hidrógeno o $(CH_2)_{1-4}CO_2H$;

R_4 es hidrógeno o alquilo de $C_{(1-3)}$ opcionalmente interrumpido por oxígeno;

En una modalidad de la invención,

A es fenilo;

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

R_2 es hidrógeno;

B es (a);

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

R_4 es hidrógeno.

En una modalidad de la invención,

A es fenilo o piridinilo;

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

R_2 es hidrógeno;

B es (b);

R_3 es hidrógeno o $(CH_2)_{1-4}CO_2H$;

R_4 es hidrógeno.

En una modalidad de la invención,

A es fenilo o piridinilo;

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

R_2 es hidrógeno;

B es (c);

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

R_4 es hidrógeno.

En una modalidad A es fenilo. En otra modalidad, A es denilo 3,4-sustituido.

En una modalidad, R_1 es dos sustituyentes, uno de los cuales es alcoxi de $C_{(1-3)}$, el otro seleccionado de halógeno o ciano. En otra modalidad, R_1 es dos sustituyentes, uno de los cuales es isopropoxi y el otro se selecciona de cloro o ciano. En otra modalidad, R_1 es dos sustituyentes seleccionados de cloro, isopropoxi y ciano. En otra modalidad, R_1 es cloro e isopropoxi. En una modalidad adicional, R_1 es cloro en la posición 3 e isopropoxi en la posición 4 cuando A es fenilo o R_1 es cloro en la posición 5 e isopropoxi en la posición 6 cuando A es piridinilo. En otra modalidad, R_1 es isopropoxi y ciano. En una modalidad adicional, R_1 es ciano en la posición 3 e

isopropoxi en la posición 4 cuando A es fenilo o R_1 es ciano en la posición 5 e isopropoxi en la posición 6 cuando A es piridinilo.

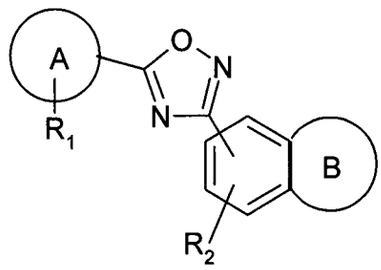
En una modalidad R_2 es hidrógeno.

En una modalidad B es (b). En otra modalidad B es (c).

En una modalidad R_3 es $(CH_2)_{1-3}CO_2H$. En otra modalidad, R_3 es $(CH_2)_3CO_2H$.

En una modalidad R_4 es hidrógeno.

La presente invención por lo tanto provee compuestos de la fórmula (IA) o una sal farmacéuticamente aceptable de los mismos:



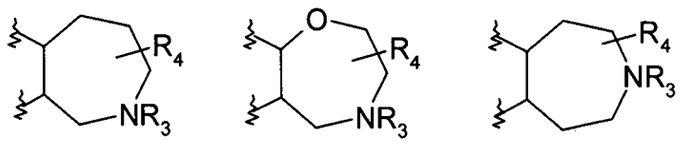
(IA)

A es fenilo o un anillo de heteroarilo de 5 ó 6 miembros;

R_1 es de hasta dos sustituyentes independientemente seleccionados de halógeno, alcoxi de$C_{(1-3)}$, fluoroalquilo de $C_{(1-3)}$, ciano, fenilo opcionalmente sustituido, fluoroalcoxi de $C_{(1-3)}$, alquilo de $C_{(1-6)}$ y cicloalquilo de $C_{(3-6)}$;

R_2 es hidrógeno, halógeno o alquilo de $C_{(1-4)}$;

B es un anillo saturado de 7 miembros seleccionado de los siguientes:



(a) (b) (c)

R_3 es hidrógeno o $(CH_2)_{1-4}CO_2H$;

R_4 es hidrógeno o alquilo de $C_{(1-3)}$ opcionalmente interrumpido por oxígeno;

En una modalidad de la invención,

A es fenilo; y/o

R_1 es de 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 o $(CH_2)_{1-3}CO_2H$; y/o

R_4 es hidrógeno.

En una modalidad de la invención,

A es fenilo; y/o

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

R_2 es hidrógeno; y/o

B es (b); y/o

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

R_4 es hidrógeno.

En una modalidad de la invención,

A es fenilo; y/o

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

R_2 es hidrógeno; y/o

B es (c); y/o

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

R_4 es hidrógeno.

El término "alquilo", como un grupo o parte de un grupo, v.gr., alcoxi o hidroxialquilo se refiere a un grupo alquilo de cadena recta o ramificada en todas las formas isoméricas. El término "alquilo de $C_{(1-6)}$" se refiere a un grupo alquilo, como se definió antes, que contiene por lo menos 1, y cuando mucho 6 átomos de carbono. Ejemplos de dichos grupos alquilo incluyen metilo, etilo, propilo, *iso*-propilo, *n*-butilo, *iso*-butilo, *sec*-butilo o *ter*-butilo. Ejemplos de dichos grupos alcoxi incluyen metoxi, etoxi, propoxi, *iso*-propoxi, butoxi, *iso*-butoxi, *sec*-butoxi and *ter*-butoxi.

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

Como se usa aquí, 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

anillos heteroarilo de 5 ó 6 miembros incluyen pirrolilo, triazolilo, tiadiazolilo, tetrazolilo, imidazolilo, pirazolilo, isotiazolilo, tiazolilo, isoxazolilo, oxazolilo, oxadiazolilo, furazanilo, furanilo, tienilo, piridilo, pirimidinilo, pirazinilo, piridazinilo y triazinilo.

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

Ciertos de los compuestos en la presente pueden existir en varias formas tautoméricas y se debe entender que la invención abarca todas esas formas tautoméricas.

Cabe entender que ciertos compuestos de la invención contienen grupos tanto ácidos como básicos y por lo tanto pueden existir como zwitteriones a ciertos valores de pH.

Compuestos adecuados de la invención son:

7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1H-2-benzazepina

ácido [7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]acético

2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1H-2-benzazepin-7-il)-1,2,4-oxadiazol-5-il]benzonitrilo

ácido [7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]acético

ácido 4-[7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]butanoico

ácido 3-[7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]propanoico

2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1H-3-benzazepin-6-il)-1,2,4-oxadiazol-5-il]benzonitrilo

6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1H-3-benzazepina

ácido 3-[6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]propanoico

ácido [6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]acético

6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1H-2-benzazepina

ácido [6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]acético

8-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-

tetrahidro-1,4-benzoxazepina

ácido 3-[8-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoico

ácido 4-[8-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]butanoico

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

7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1H-3-benzazepina

2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)-1,2,4-oxadiazol-5-il]benzonitrilo

7-{5-[4-[(1-metiletil)oxi]-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-2,3,4,5-tetrahidro-1H-3-benzazepina

7-{5-[2-(trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-2,3,4,5-tetrahidro-1H-3-benzazepina

ácido 3-[7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]propanoico

ácido [7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]acético

ácido [7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]acético

ácido (7-{5-[4-[(1-metiletil)oxi]-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il)acético

ácido (7-{5-[2-(trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il)acético

ácido 4-[7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]butanoico

ácido 4-[7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]butanoico

ácido 4-(7-{5-[4-[(1-metiletil)oxi]-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il)butanoico

ácido 4-(7-{5-[2-(trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il)butanoico

2-(Metiloxi)-5-[3-(2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)-1,2,4-oxadiazol-5-il]benzonitrilo

9-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1,4-benzoxazepina

2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1,4-benzoxazepin-9-il)-1,2,4-oxadiazol-5-il]benzonitrilo

ácido 4-[9-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]butanoico

ácido 4-[9-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]butanoico

2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1,4-benzoxazepin-7-il)-1,2,4-oxadiazol-5-il]benzonitrilo

clorhidrato de 7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-

oxadiazol-3-il)-2,3,4,5-tetrahidro-1,4-benzoxazepina

ácido 3-[7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoico

ácido 3-[7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoico

ácido 4-[7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]butanoico

ácido 4-[7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]butanoico

2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1,4-benzoxazepin-8-il)-1,2,4-oxadiazol-5-il]benzonitrilo

ácido 4-[8-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]butanoico

ácido 5-[9-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]pentanoico

ácido [9-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]acético

ácido 3-[9-(5-{5-cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoico

ácido 3-[9-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoico

ácido 3-[9-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoico

formiato de 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)-1,2,4-oxadiazol-5-il]-3-piridincarbonitrilo

clorhidrato de 7-(5-{5-cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1*H*-3-benzazepina

ácido 4-[7-(5-{5-cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]butanoico

o sales farmacéuticamente aceptables de los mismos.

En una modalidad de la invención un compuesto de la fórmula (I) es ácido 4-[7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]butanoico o una sal farmacéuticamente aceptables de los mismos.

En otra modalidad de la invención un compuesto de la fórmula (I) es ácido 4-[9-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]butanoico o una sal farmacéuticamente aceptables de los mismos.

Derivados farmacéuticamente aceptables de compuestos de la fórmula (I) incluyen cualquier sal farmacéuticamente aceptable, éster o sal de dicho éster de un compuesto de la fórmula (I) que, al administrarse al receptor es capaz de proveer (directamente o indirectamente) un compuesto de la fórmula (I) o un metabolito activo o residuo del mismo.

Los compuestos de la fórmula (I) pueden formar sales. Se apreciará que para usarse en medicina, las sales de los compuestos de la fórmula (I) deben ser farmacéuticamente aceptables. Las sales

farmacéuticamente aceptables adecuadas serán evidentes para los expertos en la técnica e incluyen aquellas descritas en J. Pharm. Sci., 1977, 66, 1-19, tales como sales ácidas de adición formadas con ácidos inorgánicos, v.gr., ácido clorhídrico, bromhídrico, sulfúrico, nítrico o fosfórico; y ácidos orgánicos v.gr., ácido succínico, maleico, acético, fumárico, cítrico, tartárico, benzoico, p-toluensulfónico, metansulfónico o naftalensulfónico. Ciertos de los compuestos de la fórmula (I) pueden formar sales ácidas de adición con uno o más equivalentes del ácido. La presente invención incluye, dentro de su alcance, todas las posibles formas estequiométricas y no estequiométricas. Las sales también se pueden preparar a partir de bases farmacéuticamente aceptables incluyendo bases inorgánicas y orgánicas. Sales derivadas de bases inorgánicas incluyen aluminio, amonio, calcio, cobre, férricas, ferrosas, litio, magnesio, sales mangánicas, manganosas, potasio, sodio, zinc, y similares. Las sales derivadas de bases orgánicas farmacéuticamente aceptables incluyen sales de aminas primarias, secundarias y terciarias; aminas sustituidas incluyendo aminas que ocurren naturalmente; y aminas cíclicas. Las bases orgánicas farmacéuticamente aceptables particulares incluyen arginina, betaína, cafeína, colina, N,N'-dibenciletilendiamina, dietilamina, 2-dietilaminoetanol, 2-dimetilaminoetanol, etanolamina, etilenediamina, N-etil-morfolina, N-etilpiperidina, glucamina, glucosamina, histidina, hidrabamina, isopropilamina, lisina, metilglucamina, morfolina, piperazina, piperidina, procaína, purinas, teobromo, trietilamina, trimetilamina, tripropilamina, tris(hidroximetil)aminometano (TRIS, trometamol) y similares. Las sales

también se pueden formar 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 orgánicos. Dichos ácidos incluyen ácido acético, bencensulfónico, benzoico, alcanforsulfónico, cítrico, etansulfónico, etandisulfónico, fumárico, glucónico, glutámico, bromhídrico, clorhídrico, isetiónico, láctico, maleico, malico, mandélico, metansulfónico, múcico, pamoico, pantoténico, fosfórico, propiónico, succínico, sulfúrico, tartárico, p-toluensulfónico, y similares.

Las sales ácidas de adición farmacéuticamente aceptables se pueden preparar convencionalmente por reacción con el ácido o derivado de ácido apropiado. Las sales farmacéuticamente aceptables con bases se pueden preparar convencionalmente por reacción con la base inorgánica u orgánica apropiada.

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

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

Las potencias y eficacias de los compuestos de esta invención para el receptor de S1P1 se pueden determinar por prueba de GTPγS realizada sobre receptor clonado humano como se describe aquí. Los compuestos de la fórmula (I) han mostrado actividad agonista sobre el receptor de S1P1, usando pruebas funcionales descritas aquí.

Las potencias y eficacias de los compuestos de esta invención para el receptor de S1P1 se pueden determinar por prueba de GTPγS realizada sobre receptor clonado humano como se describe aquí. Los compuestos de la fórmula (I) han mostrado actividad agonista sobre el receptor de S1P1, usando pruebas funcionales descritas aquí.

Los compuestos de la fórmula (I) y sus sales farmacéuticamente aceptables por lo tanto se usan en el tratamiento de condiciones o trastornos que son mediados por el receptor de S1P1. En particular, los compuestos de la fórmula (I) y sus sales farmacéuticamente aceptables se usan 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 de isquemia-reperfusión, tumores sólidos, y metástasis de tumor, enfermedades asociadas con angiogénesis, enfermedades vasculares, condiciones de dolor, enfermedades virales agudas, condiciones intestinales inflamatorias, diabetes dependiente de insulina y no dependiente de insulina (de aquí en adelante referidos como "trastornos de la invención").

Los compuestos de la fórmula (I) y sus sales farmacéuticamente

aceptables por lo tanto se usan en el tratamiento de lupus eritematoso.

Los compuestos de la fórmula (I) y sus sales farmacéuticamente aceptables por lo tanto se usan en el tratamiento de psoriasis.

Los compuestos de la fórmula (I) y sus sales farmacéuticamente aceptables por lo tanto se usan en el tratamiento de esclerosis múltiple.

Cabe entender que "tratamiento", como se usa aquí, incluye profilaxis, así como alivio de síntomas establecidos.

Por lo tanto, la invención también provee compuestos de la fórmula (I) o sales farmacéuticamente aceptables de los mismos, para usarse como sustancias terapéuticas, en particular en el tratamiento de las condiciones o trastornos mediados por el receptor de S1P1. En particular, la invención provee un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable de los mismos para usarse como una sustancia terapéutica 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 de isquemia-reperfusión, tumores sólidos y metástasis de tumor, enfermedades asociadas con angiogénesis, enfermedades vasculares, condiciones de dolor, enfermedades virales agudas, condiciones intestinales inflamatorias, diabetes dependiente de insulina y no dependiente de insulina.

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

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

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

La invención además provee un método de tratamiento de condiciones o trastornos en mamíferos incluyendo humanos que pueden ser mediados por el receptor de S1P1, que comprende administrar al paciente una cantidad terapéuticamente segura y efectiva de un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable de los mismos. En particular, la invención provee un método de tratamiento de esclerosis múltiple, enfermedades autoinmunes, trastornos inflamatorios crónicos, asma, neuropatías inflamatorias, artritis, trasplante, enfermedad de Crohn, colitis ulcerativa, lupus eritematoso, psoriasis, lesión de isquemia-reperfusión, tumores sólidos y metástasis de tumor, enfermedades asociadas con angiogénesis, enfermedades vasculares, condiciones de dolor, enfermedades virales agudas, condiciones intestinales inflamatorias, diabetes dependiente de insulina y no dependiente de insulina, que comprende administrar al paciente una cantidad terapéuticamente segura y efectiva de un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable de los mismos.

La invención provee un método de tratamiento de lupus eritematoso, que comprende administrar al paciente una cantidad

terapéuticamente segura y efectiva de un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable de los mismos.

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

La invención provee un método de tratamiento de esclerosis múltiple, que comprende administrar al paciente una cantidad terapéuticamente segura y efectiva de un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable de los mismos.

En otro aspecto, la invención provee el uso de un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable de los mismos en la fabricación de un medicamento para usarse en el tratamiento de las condiciones o trastornos mediados por el receptor de S1P1.

En particular la invención provee un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable de los mismos para usarse en la fabricación de un medicamento para usarse 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 de isquemia-reperfusión, tumores sólidos, and metástasis de tumor, enfermedades asociadas con angiogénesis, enfermedades vasculares, condiciones de dolor, enfermedades virales agudas, condiciones intestinales inflamatorias, diabetes dependiente

de insulina y no dependiente de insulina.

Los compuestos de la fórmula (I) y sus sales farmacéuticamente aceptables se usan en la fabricación de un medicamento para usarse en el tratamiento de lupus eritematoso.

Los compuestos de la fórmula (I) y sus sales farmacéuticamente aceptables se usan en la fabricación de un medicamento para usarse en el tratamiento de psoriasis.

Los compuestos de la fórmula (I) y sus sales farmacéuticamente aceptables se usan en la fabricación de un medicamento para usarse en el tratamiento de esclerosis múltiple.

A fin de usarse los compuestos de la fórmula (I) y sales farmacéuticamente aceptables de los mismos en terapia, normalmente se formulan en una composición farmacéutica de conformidad con práctica farmacéutica estándar. La presente invención también provee una composición farmacéutica, que comprende un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable de los mismos, y un vehículo o excipiente farmacéuticamente aceptable.

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

Una composición farmacéutica de la invención, que se puede

preparar mediante mezclado, adecuadamente a temperatura ambiente y presión atmosférica, está usualmente adaptada para administración oral, parenteral o rectal y, como tal, puede estar en forma de tabletas, cápsulas, preparaciones líquidas orales, polvos, gránulos, pastillas, polvos reconstituibles, soluciones o suspensiones inyectables o infundibles o supositorios. Las composiciones oralmente administrables son generalmente preferidas.

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

Las preparaciones líquidas orales pueden estar en forma de, por ejemplo, suspensiones, soluciones y emulsiones acuosas u oleosas, jarabes o elíxires, o pueden estar en forma de un producto seco para reconstitución con agua u otro vehículo adecuado antes de usarse. Dichas preparaciones líquidas pueden contener aditivos convencionales tales como agentes de suspensión (v.gr., jarabe de sorbitol, derivados de celulosa o grasas comestibles hidrogenadas), agentes emulsionantes (v.gr., lecitina o acacia),

vehículos no acuosos (que pueden incluir aceites comestibles, v.gr., aceite de almendra, ésteres de aceite, alcohol etílico o aceites vegetales fraccionados), conservadores (v.gr., metil o propil-p-hidroxibenzoatos o ácido sórbico) y, si se desea, saborizantes y colorantes convencionales, sales reguladoras de pH y agentes edulcorantes según sea apropiado. Las preparaciones para administración oral se pueden formular adecuadamente para dar liberación controlada del compuesto activo.

Para administración parenteral, las formas de dosis unitarias se preparan utilizando un compuesto de la invención o sales farmacéuticamente aceptables del mismo y un vehículo estéril. Las formulaciones para inyección pueden estar presentadas en forma de dosis unitaria v.gr., en ampolletas o en dosis múltiples, utilizando un compuesto de la invención o derivados farmacéuticamente aceptable del mismo y un vehículo estéril, opcionalmente con un conservador añadido. Las composiciones pueden adoptar formas tales como suspensiones, soluciones o emulsiones en vehículos oleosos o acuosos, y pueden contener agentes formuladores tales como agentes de suspensión, estabilización y/o dispersión. Alternativamente, el ingrediente activo puede estar en forma de polvo para constitución con un vehículo adecuado, v.gr., agua libre de pirógenos estéril, antes de usarse. El compuesto, dependiendo del vehículo y concentración usados, puede ser ya sea suspendido o disuelto en el vehículo. En la preparación de soluciones, el compuesto se puede disolver para inyección y esterilizarse en filtro antes de llenar un frasco adecuado o ampolleta con el mismo y sellar. Ventajosamente,

adyuvantes tales como un anestésico local, conservadores y agentes reguladores de pH se disuelven en el vehículo. Para incrementar la estabilidad, la composición puede ser congelada después de llenar con ella el frasco y de remover el agua bajo vacío. Las suspensiones parenterales se preparan sustancialmente de la misma manera, excepto que el compuesto es suspendido en el vehículo en lugar de ser disuelto, y la esterilización no se puede lograr por filtración. El compuesto puede ser esterilizado exponiéndolo a óxido de etileno antes de la suspensión en un vehículo estéril. Ventajosamente, un agente tensoactivo o agente humectante es incluido en la composición para facilitar la distribución uniforme del compuesto.

Las lociones se pueden formular con una base acuosa u oleosa y en general también contendrá uno o más agentes emulsionantes, agentes estabilizadores, agentes dispersantes, agentes de suspensión, agentes espesantes o agentes colorantes. Las gotas se pueden formular con una base acuosa o no acuosa que también comprende uno o más agentes dispersantes, agentes estabilizadores, agentes solubilizantes o agentes de suspensión. También pueden contener un conservador.

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

Los compuestos de la fórmula (I) o sales farmacéuticamente

aceptables de los mismos también se pueden formular como preparaciones de deposición. Dichas formulaciones de larga acción se pueden administrar por implantación (por ejemplo, subcutáneamente o intramuscularmente) o por 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 escasamente solubles, por ejemplo, como una sal escasamente soluble.

Para administración intranasal, los compuestos de la fórmula (I) o sales farmacéuticamente aceptables de los mismos, se puede formular como soluciones para administración mediante un dispositivo de dosis medida o unitaria adecuado o alternativamente como una mezcla en polvo con un vehículo adecuado par administración usando un dispositivo de suministro adecuado. Por lo tanto, los compuestos de la fórmula (I) o sales farmacéuticamente aceptables de los mismos se pueden formular para administración oral, bucal, parenteral, tópica (incluyendo oftálmica y nasal), deposición 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 la fórmula (I) o sales farmacéuticamente aceptables de los mismos se pueden formular para administración tópica en forma de pomadas, cremas, geles, lociones, pesarios, aerosoles o gotas (v.gr., gotas para los ojos, oídos o nariz). Pomadas y cremas, por ejemplo, se pueden formular con una base acuosa o base oleosa con la adición de

agentes espesantes y/o gelificantes adecuados. Las pomadas para administrarse a los ojos se pueden fabricar de una manera estéril usando componentes esterilizados.

La composición puede contener de 0.1% a 99% en peso, preferiblemente de 10 a 60% en peso, del material activo, dependiendo del método de administración. La dosis del compuesto usado en el tratamiento de los trastornos antes mencionados variará de la manera usual con la severidad de los trastornos, el peso del paciente, y otros factores similares. Sin embargo, como una guía general, las dosis unitarias adecuadas pueden ser de 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 la fórmula (I) o sales farmacéuticamente aceptables de los mismos se pueden usar en preparaciones de combinaciones, en combinación con otros ingredientes activos. Por ejemplo, los compuestos de la invención se pueden usar en combinación con ciclosporina A, metotrexato, esteriodes, rapamicina, citosina proinflamatoria, inmunomoduladores incluyendo sustancias biológicas u otros compuestos terapéuticamente activos.

La presente invención también incluye compuestos isotópicamente marcados, que son idénticos a aquellos mencionados 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

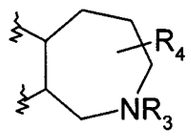
diferente de la masa atómica o número de masa usualmente encontrado en la naturaleza. Ejemplos de isótopos que pueden ser incorporados en los compuestos de la invención incluyen isótopos de hidrógeno, carbono, nitrógeno, oxígeno, fósforo, flúor, yodo y cloro, tales como ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{123}I e ^{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 están dentro del alcance de la presente invención. Los compuestos isotópicamente marcados de la presente invención, por ejemplo aquellos en los cuales los isótopos radioactivos tales como ^{3}H, ^{14}C son incorporados, son útiles en pruebas de distribución de fármacos y/o sustrado en el tejido. Isótopos tritiados, es decir, ^{3}H, y carbono-14, es decir, ^{14}C, los isótopos son particularmente preferidos por su facilidad de preparación y detectabilidad. Los isótopos de ^{11}C y ^{8}F son particularmente útiles en PET (tomografía por emisión de positrones), e isótopos de ^{125}I son particularmente útiles en SPECT (tomografía computarizada por emisión de fotones individuales), todos útiles en estudios de imágenes del cerebro. Además, la sustitución con isótopos másd pesados tales como deuterio, es decir, ^{2}H, pueden soportar ciertas ventajas terapéuticas que resultan de mayor estabilidad metabólica, por ejemplo, vida media *in vivo* incrementada o requerimientos de dosis reducidos y, por lo tanto, pueden ser preferidos en algunas circunstancias. Los compuestos isotópicamente marcados de la fórmula (I) y siguiendo esta

invención, generalmente se pueden preparar llevando a cabo los procedimientos descritos en los esquemas y/o en los siguientes ejemplos, usando un reactivo isotópicamente marcado fácilmente disponible en vez de un reactivo no isotópicamente marcado.

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

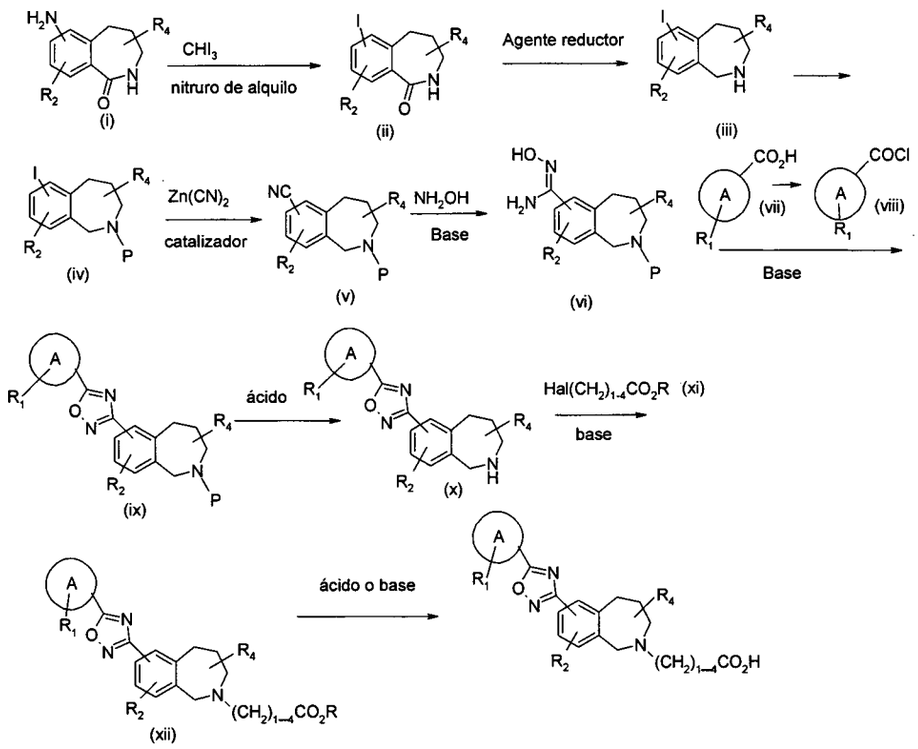
Una vía que se puede usar para preparar compuestos de la fórmula (I) cuando B es



(a)

se ilustra en el esquema 1 en donde R_1,R_2 R_4 y A se describen en la fórmula (I) excepto que R_2 no es cloro, bromo o yodo, R es álcali (por ejemplo, etilo, t-butilo) y hal es cloro, bromo o yodo.

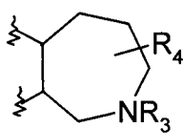
ESQUEMA 1



Los compuestos de la fórmula (i) que están comercialmente disponibles o se pueden preparar mediante un número de vías (v.gr., Johnson, Paul D.; *et al*; Bioorganic & Medicinal Chemistry Letters (2003), 13(23), 4197-4200), se pueden convertir a compuestos de la fórmula (ii) mediante tratamiento con yodoformo en presencia de un nitrito adecuado tal como nitrito de ter-butilo en un solvente adecuado tal como tetrahidrofurano (THF). Los compuestos de la fórmula (ii) se pueden convertir a compuestos de la fórmula (iii) mediante tratamiento con un agente reductor apropiado tal como diborano o hidruro de litio-aluminio en un solvente tal como THF a una

temperatura elevada tal como 80°C. Los compuestos de la fórmula (iii) se pueden convertir a un derivado protegido (iv), en donde P representa un grupo protector adecuado tal como t-butiloxi carbonilo (BOC), por ejemplo mediante tratamiento con dicarbonato de bis(1,1-dimetiletilo) en presencia de una base tal como trietilamina en un solvente adecuado tal como diclorometano (DCM). Los compuestos de la fórmula (iv) se pueden convertir a compuestos de la fórmula (v) mediante tratamiento con una fuente de cianuro adecuada tal como cianuro de zinc en presencia de un catalizador tal como tetrakistrifenilfosfino paladio (0) en un solvente adecuado tal como dimetilformamida (DMF) a una temperatura elevada tal como 80°C. Los compuestos de la fórmula (v) se pueden convertir a compuestos de la fórmula (vi) mediante tratamiento con clorhidrato de hidroxilamina y una base apropiada, tal como bicarbonato de sodio, en un solvente tal como metanol o etanol a una temperatura elevada tal como 60°C. Los compuestos de la fórmula (vi) se pueden convertir a compuestos de la fórmula (ix) mediante tratamiento con un cloruro de ácido carboxílico de la fórmula (viii) en presencia de una base tal como trietilamina en un solvente adecuado tal como DMF. Esas reacciones típicamente se agitan durante un periodo de tiempo a temperatura ambiente, después a temperaturas elevadas, tal como 120°C. Cloruros ácidos de la fórmula (viii) están ya sea comercialmente disponibles o se pueden preparar a partir del ácido correspondiente (vii) por medios convencionales. Alternativamente, los compuestos de la fórmula (vi) se pueden convertir a compuestos de la fórmula (ix) mediante tratamiento con un

ácido carboxílico de la fórmula (vii) en presencia de un agente acoplador de amida adecuado tal como clorhidrato de 1-(3-dimetilaminopropil)-N'-etilcarbodiimida (EDAC) y 1-hidroxibenzotriazol (HOBT) en un solvente adecuado tal como DMF. Esas reacciones típicamente se llevan a cabo a temperatura elevada, tal como 50-80°C. Típicamente, el ácido (vii), EDAC y HOBt se agitan durante un periodo de tiempo a temperatura ambiente antes de la adición del compuesto de la fórmula (vi). Los compuestos de la fórmula (ix), en donde P=BOC, se pueden convertir a compuestos de la fórmula (x) mediante tratamiento con un ácido adecuado, típicamente ácido trifluoroacético o ácido clorhídrico en un solvente adecuado tal como 1,4-dioxano. Los compuestos de la fórmula (x) se pueden convertir a compuestos de la fórmula (xii) mediante tratamiento con un agente alquilante (xi) en presencia de una base tal como carbonato de cesio en un solvente tal como DMF o acetonitrilo. Esas reacciones se pueden llevar a cabo a temperatura elevada, tal como 70°C. Los agentes alquilantes (xi) típicamente están comercialmente disponibles o se pueden preparar usando métodos estándares. Los compuestos de la fórmula (xii) se pueden convertir en ciertos compuestos de la fórmula (I) en donde B es

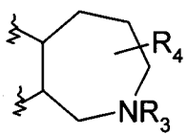


(a)

y R_3 representa $(CH_2)_{1-4}CO_2H$ mediante tratamiento con una base tal como hidróxido de sodio acuoso en un solvente alcohólico tal

como etanol o metanol. Un co-solvente, tal como THF, se puede añadir para ayudar a la disolución. La reacción de hidrólisis se puede llevar a cabo a temperatura ambiente o a una temperatura elevada tal como 50-80°C. Alternativamente, esta transformación se puede llevar a cabo usando hidróxido de sodio sólido en etanol en un reactor de microondas a una temperatura tal como 100°C o en donde R=t-butilo, con ácido trifluoroacético (TFA) o HCl.

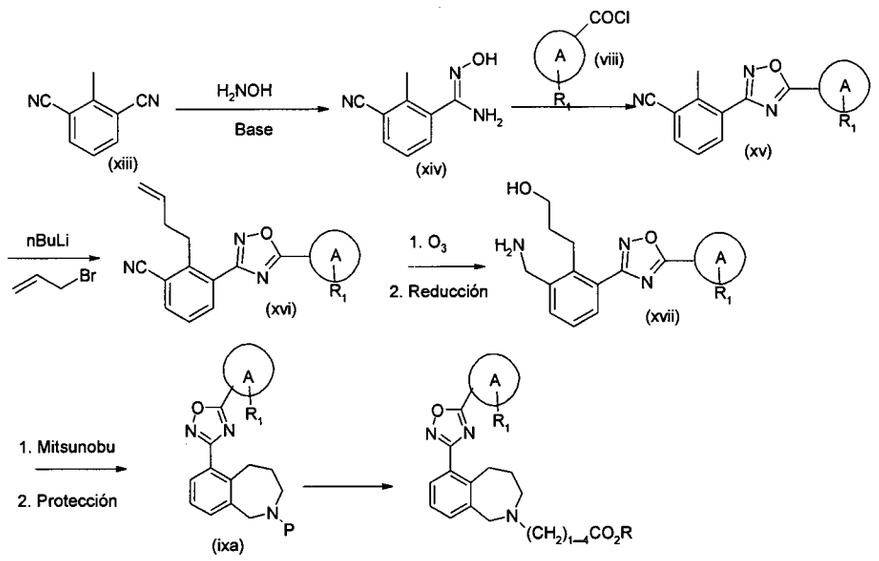
Los compuestos de la fórmula (I) en donde R_2 y R_4 son ambos hidrógeno, B es



(a)

R_3 es $(CH_2)_{1-4}CO_2H$, R_1, y A son como se define en la fórmula (I) y la porción oxadiazol es unida a la porción benzazepina en la posición 6 se puede preparar alternativamente por la vía ilustrada en el esquema 2.

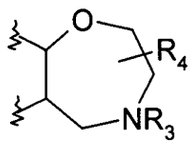
ESQUEMA 2



El compuesto comercialmente disponible de la fórmula (xiii) se puede convertir al compuesto de la fórmula (xiv) mediante tratamiento con clorhidrato de hidroxilamina como se describió en el esquema 1 para conversión de (v) a (vi). Los compuestos de la fórmula (xiv) se pueden convertir a compuestos de la fórmula (xv) mediante tratamiento con un cloruro de ácido carboxílico de la fórmula (viii) en presencia de una base tal como trietilamina como se describió en el esquema 1 para conversión de (vi) a (ix). Los compuestos de la fórmula (xv) se pueden convertir a compuestos de la fórmula (xvi) mediante tratamiento con una base apropiada tal como n-butillitio seguido por bromuro de alilo en un solvente tal como THF a temperaturas reducidas tal como -78°C. Los compuestos de la fórmula (xvi) se pueden convertir a compuestos de la fórmula (xvii) mediante tratamiento con ozono en

un solvente adecuado tal como DCM, a una temperatura reducida tal como -78°C seguido por reducción usando un agente reductor adecuado tal como complejo de borano – sulfuro de dimetilo en un solvente adecuado tal como THF. Los compuestos de la fórmula (xvii) se pueden convertir a compuestos de la fórmula (ix), típicamente por ciclización bajo condiciones de Mitsunobu por ejemplo usando azodicarboxilato de diisopropil (DIAD) y trifenilfosfino en un solvente adecuado tal como DCM, seguido por la incorporación de un grupo protector adecuado en el nitrógeno de la benzazepina, tal como BOC, como se describió en el esquema 1 para conversión de (iii) a (iv). Los compuestos de la fórmula (ixa) se pueden convertir a compuestos de la fórmula (I) como se describió en el esquema 1 para conversión de (ix) a ciertos compuestos de la fórmula (I)

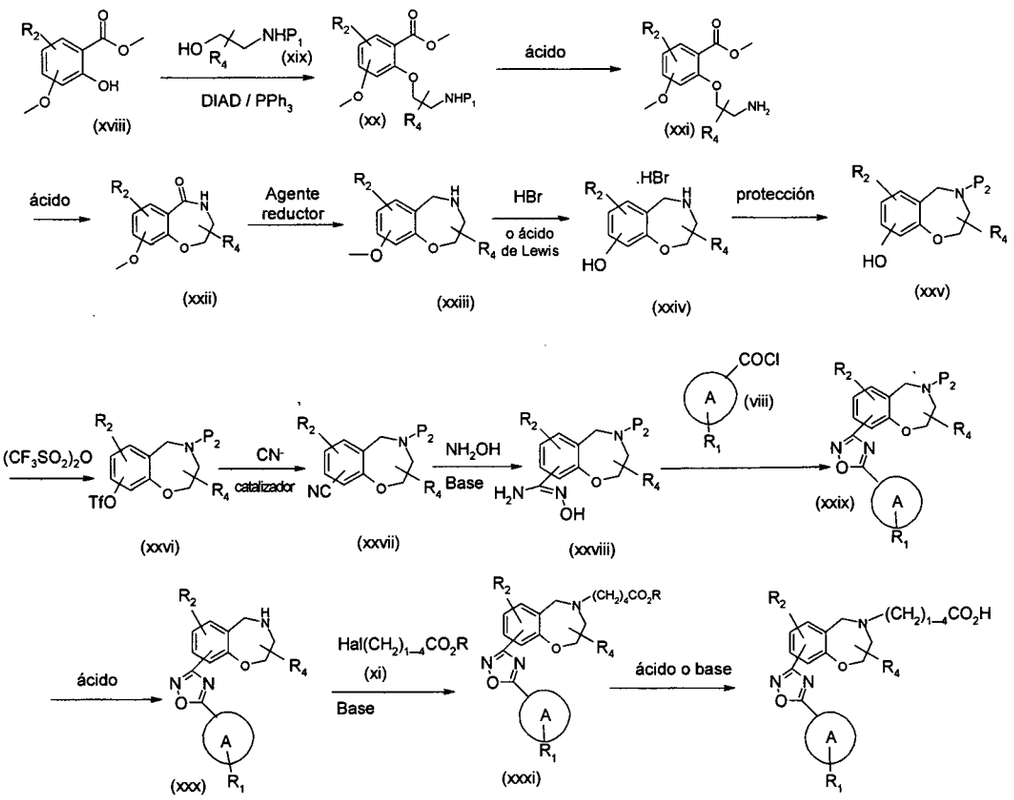
Una vía que se puede usar para preparar compuestos de la fórmula (I) en donde B es



(b)

R_3 es $(CH_2)_{1-4}CO_2H$, R_1, R_2, R_4 y A son como se define en la fórmula (I) excepto que R_2 no es cloro, bromo o yodo, R es alquilo (por ejemplo metilo, t-butilo) y Hal es cloro, bromo o yodo.

ESQUEMA 3



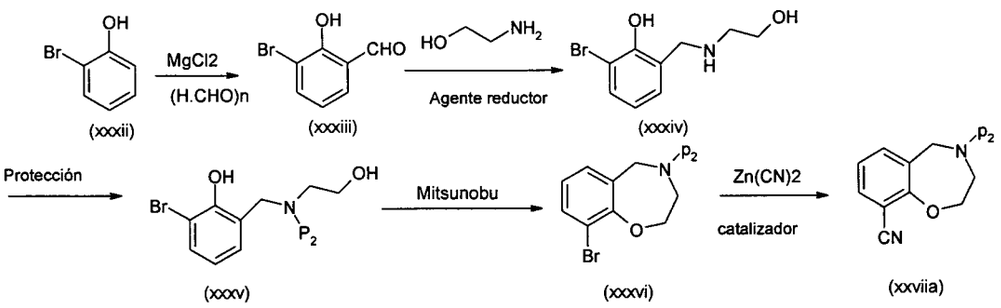
Los compuestos de la fórmula (xviii) que están ya sea comercialmente disponibles (v.gr., Aldrich) o se pueden preparar usando métodos estándares, se pueden convertir a compuestos de la fórmula (xx), típicamente mediante reacción con una etanolamina protegida (xix) en donde P_1 representa un grupo protector adecuado tal como BOC, bajo condiciones de Mitsunobu usando, por ejemplo DIAD y trifenilfosfina en un solvente adecuado tal como THF. Los compuestos de la fórmula (xx) se pueden convertir a compuestos de la fórmula (xxi) y/o (xxii) mediante tratamiento con ácido, típicamente ácido trifluoroacético o ácido clorhídrico. Los compuestos

de la fórmula (xxi) también se pueden convertir a compuestos de la fórmula (xxii) por calentamiento en un solvente apropiado tal como tolueno a temperaturas elevadas tales como 80°C. Los compuestos de la fórmula (xxii) se pueden convertir a compuestos de la fórmula (xxiii) mediante tratamiento con un agente reductor apropiado tal como hidruro de litio-aluminio a una temperatura baja tal como por debajo de 15°C, en un solvente tal como THF, después elevando la temperatura por ejemplo a 80°C. Los compuestos de la fórmula (xxiii) se pueden convertir a compuestos de la fórmula (xxiv) mediante tratamiento con un ácido de Lewis tal como tribromuro de boro o un ácido fuerte tal como HBr.

Los compuestos de la fórmula (xxiv) se pueden convertir a un derivado protegido (xxv), en donde P_2 representa un grupo protector adecuado tal como t-butiloxi carbonilo (BOC), como se describió en el esquema 1 para conversión de (iii) a (iv). Los compuestos de la fórmula (xxv) se pueden convertir a compuestos de la fórmula (xxvi) mediante tratamiento con anhídrido trifluorometansulfónico en un solvente apropiado tal como piridina. Los compuestos de la fórmula (xxvi) se pueden convertir a compuestos de la fórmula (xxvii) mediante tratamiento con un cianuro adecuado tal como cianuro de zinc en presencia de un catalizador tal como tetrakistrifenilfosfino paladio (0) en un solvente adecuado tal como DMF. Los compuestos de la fórmula (xxvii) se pueden convertir a compuestos de la fórmula (I) usando métodos análogos a aquellos descritos para la conversión de compuestos de la fórmula (v) a compuestos de la fórmula (I) (esquema 1).

Una vía alternativa para el intermediario (xxvii) en donde el grupo ciano está en la posición 9 y P_2 representa un grupo protector adecuado tal como BOC, y R_2 y R_4 son hidrógeno (representado por la fórmula (xxviia) se ilustra en el esquema 4.

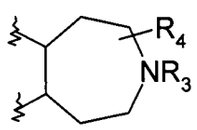
ESQUEMA 4



El compuesto de la fórmula (xxxii) se puede convertir al compuesto de la fórmula (xxxiii) mediante tratamiento con paraformaldehído y cloruro de magnesio seco en un solvente apropiado tal como THF con calentamiento bajo reflujo. Los compuestos de la fórmula (xxxiii) se pueden convertir a compuestos de la fórmula (xxxiv) mediante tratamiento con etanolamina en presencia de un agente reductor tal como triacetoxiborhidruro de sodio. Los compuestos de la fórmula (xxxiv) se pueden convertir a un derivado protegido (xxxv), en donde P_2 representa un grupo protector adecuado tal como BOC como se describió en el esquema 1 para conversión de (iii) a (iv). Los compuestos de la fórmula (xxxv) se pueden convertir a compuestos de la fórmula (xxxvi), típicamente por ciclización bajo condiciones

de Mitsunobu usando, por ejemplo azodicarboxilato de diisopropil (DIAD) y trifenilfosfina en un solvente adecuado tal como THF. Los compuestos de la fórmula (xxxvi) se pueden convertir a compuestos de la fórmula (xxviia) mediante tratamiento con una fuente de cianuro adecuada tal como cianuro de zinc como se describió en el esquema 1 para conversión de (iv) a (v).

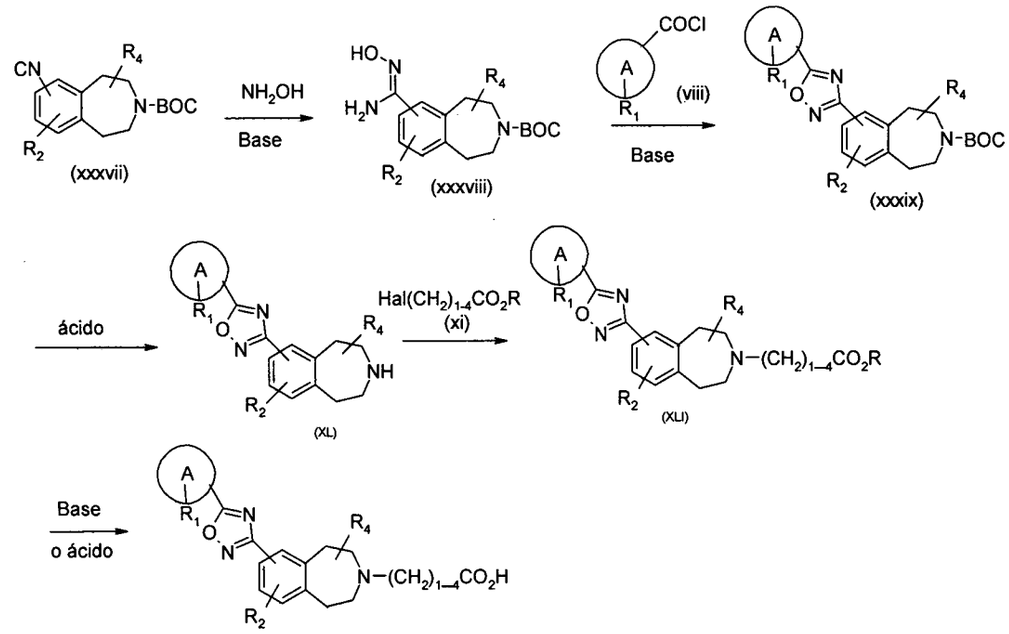
Una vía que se puede usar para preparar compuestos de la fórmula (I), en donde R_1, R_2, R_4 y A son como se describe en la fórmula (I), R_3 representa $(CH_2)_{1-4}CO_2H$ y B es



(c)

se ilustra en el esquema 5. R es alquilo (por ejemplo etilo, t-butilo) y Hal es cloro, bromo o yodo.

ESQUEMA 5



Los compuestos de la fórmula (xxxvii) por ejemplo, en donde el grupo ciano está en la posición 7 (preparado por ejemplo, usando el método descrito en Micheli, F. *et al.* Journal of Medicinal Chemistry (2007), 50(21), 5076-5089), se pueden convertir a compuestos de la fórmula (I) usando métodos análogos a aquellos descritos para la conversión de compuestos de la fórmula (v) a compuestos de la fórmula (I) (esquema 1).

Todas las publicaciones, incluyendo pero sin limitarse a patentes y solicitudes de patente, citadas en la especificación se incorporan aquí por referencia como si cada publicación individual fuera específicamente e individualmente indicada para ser incorporada aquí por referencia como si se expusiera en su totalidad.

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

Abreviaturas

g–		gramos
mg –		miligramos
ml –		mililitros
ul –		microlitros
BOC_2O –		dicarbonato de bis(1,1-dimetiletilo)
MeCN –		acetonitrilo
MeOH –		metanol
EtOH –		etanol
Et2O –		éter dietílico
EtOAc –		acetato de etilo
DCM –		diclorometano
DIAD –		azodicarboxilato de diisopropilo
DIPEA –		diisopropiletilamina
DME –		1,2-bis(metiloxi)etano
DMF –		N,N-dimetilformamida
DMSO–		sulfóxido de dimetilo
d_6DMSO–		sulfóxido de dimetilo deuterado
EDAC –		clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida
EDC –		clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida

EDCI – clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida

HOBT/HOBt – Hidroxibenzotriazol

IPA – alcohol isopropílico

MeOD – metanol deuterado

NCS – N-clorosuccinimida

PPh_3 – Trifenilfosfina

PyBOP – hexafluorofosfato de benzotriazol-1-il-oxitripirrolidinofosfonio

THF – tetrahidrofurano

TFA - ácido trifluoroacético

dba – dibencilidenacetona

T.A. – temperatura ambiente

°C – grados centígrados

M – Molar

H – protón

s – singulete

d – doblete

t – triplete

q – cuadriplete

MHz – megahertz

MeOD – metanol deuterado

CL-EM – Cromatografía de líquidos-espectrometría de masa

CL/EM– Cromatografía de líquidos/espectrometría de masa

EM – Espectrometría de masa

EA – Electroaspersión

MH+ – ion + H+ de masa

PADM – Cromatografía de líquidos preparativa automatizada dirigida a la masa

sat. – saturada

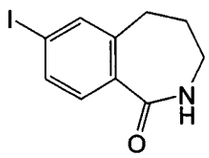
SCX – cromatografía de intercambio de cationes de fase sólida

Sección de química general

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

PREPARACION 1

7-Yodo-2,3,4,5-tetrahidro-1*H*-2-benzazepin-1-ona



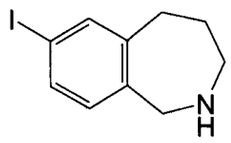
7-Amino-2,3,4,5-tetrahidro-1H-2-benzazepin-1-ona (se puede preparar como se describe en: *Preparation of benzazepinylpyrrolidonylsulfonamides as Factor Xa inhibitors*; WO2007059952) (500 mg, 2.84 mmoles) y triyodometano (2234 mg, 5.67 mmoles) se disolvieron en THF (100 ml). Después, nitruro de 1,1-dimetiletilo

(0.675 ml, 5.67 mmoles) disuelto en THF (20 ml) se añadió gota a gota durante 20 minutos y la solución resultante se agitó durante 1 hora. La mezcla se calentó a 50°C durante 30 minutos. La mayor parte del solvente se removió por evaporación y el crudo se sometió a cromatografía biotage (EtOAc/hexano 3:1) para dar el compuesto del título (550 mg) como un sólido amarillo pálido.

EM (EA) $C_{10}H_{10}INO$ requiere 287: encontrado 287.8 $(M+H)^+$.

PREPARACION 2

7-Yodo-2,3,4,5-tetrahidro-1H-2-benzazepina



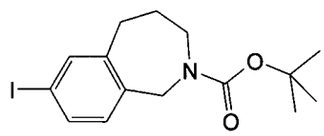
7-Yodo-2,3,4,5-tetrahidro-1H-2-benzazepin-1-ona (preparación 1) (550 mg, 1.916 mmoles) se disolvió en THF seco (70 ml) y se trató con complejo de borano-THF (1M) (11.49 ml, 11.49 mmoles) y se calentó a reflujo durante 4 horas. Después, la reacción se dejó reposar durante la noche. Complejo de borano-THF adicional (1M, 2 ml) se añadió y la reacción se calentó a reflujo temperatura durante 2 horas y 30 minutos adicionales. Metanol se añadió cuidadosamente a la mezcla de reacción enfriada. La reacción se agitó hasta que se detuvo la efervescencia. Después HCl 2N (ac.) (20 ml) se añadió cuidadosamente en porciones y, después de que ha disminuido la efervescencia, la solución se calentó a 75°C durante 30 minutos. LC/EM mostró un mayor producto. La mezcla de reacción se enfrió y se

añadió agua (20 ml). La mezcla se lavó con EtOAc (40 ml), se basificó con NaOH(ac.) 2 N y se extrajo con EtOAc (50 ml). La capa de EtOAc se secó sobre $MgSO_4$ anhidro y se evaporó para dar el compuesto del título (400 mg) como un sólido blanco.

EM (EA) $C_{10}H_{12}IN$ requiere 273: encontrado 274 $(M+H)^+$.

PREPARACION 3

7-Yodo-1,3,4,5-tetrahidro-2H-2-benzazepin-2-carboxilato de 1,1-dimetiletilo

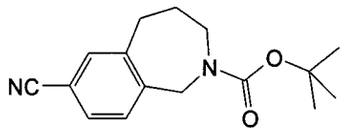


7-Yodo-2,3,4,5-tetrahidro-1H-2-benzazepina (preparación 2) (450 mg, 1.648 mmoles) se disolvió en DCM (30 ml) y se trató con BOC_2O (0.459 ml, 1.977 mmoles) seguido por trietilamina (0.459 ml, 3.30 mmoles). La mezcla de reacción se agitó a T.A. durante 30 minutos. LC/EM mostró un mayor producto. La reacción se lavó con HCl 0.5M (20 ml), $NaHCO_3$ sat.(20 ml), se secó sobre $MgSO_4$ anhidro y se evaporó para dar el compuesto del título (650 mg) como un aceite incoloro.

EM (EA) $C_{15}H_{20}INO_2$ requiere 373; encontrado 318 $(M+H-56)^+$.

PREPARACION 4

7-Ciano-1,3,4,5-tetrahidro-2H-2-benzazepin-2-carboxilato de 1,1-dimetiletilo

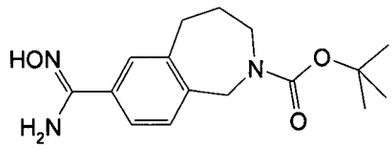


7-Yodo-1,3,4,5-tetrahidro-2H-2-benzazepin-2-carboxilato de 1,1-dimetiletilo (preparación 3) (650 mg, 1.742 mmoles), cianuro de zinc(II) (123 mg, 1.045 mmoles) y tetrakis(trifenilfosfino)paladio(0) (201 mg, 0.174 mmoles) se agitaron en DMF seca a 80°C durante 45 minutos. EtOAc (100 ml) se añadió a la reacción enfriada antes de lavar con agua (2x70 ml) y salmuera (100 ml). La capa de EtOAc se secó sobre $MgSO_4$ anhidro y se evaporó. CCD (1:3 de EtOAc/hexano) mostró 2 manchas, una con un RF muy alto. El producto crudo se sometió a cromatografía biotage (1: 3 de EtOAc/hexano) y el punto de RF más bajo se aisló. Durante la evaporación, el compuesto del título se obtuvo (350 mg) como un aceite incoloro.

EM (EA) $C_{16}H_{20}N_2O_2$ requiere 272; encontrado $217(M+H-56)^+$.

PREPARACION 5

7-[(Hidroxiamino)(imino)metil]-1,3,4,5-tetrahidro-2H-2-benzazepin-2-carboxilato de 1,1-dimetiletilo

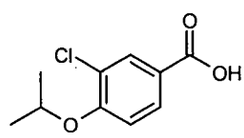


7-Ciano-1,3,4,5-tetrahidro-2H-2-benzazepin-2-carboxilato de 1,1-dimetiletilo (preparación 4) (350 mg, 1.285 mmoles), clorhidrato de hidroxilamina (223 mg, 3.21 mmoles) y bicarbonato de sodio (540 mg, 6.43 mmoles) se suspendieron en etanol (15 ml) y se agitaron a 55°C durante 5 horas. La mezcla de reacción se dejó reposar durante la noche. LC/EM mostró un producto mayor individual. Los compuestos inorgánicos se removieron por filtración, lavando bien con 10% de MeOH/DCM para disolver cualquier producto precipitado. La evaporación del solvente dio un sólido blanco. La trituración con éter dio el compuesto del título (320 mg).

EM (EA) $C_{16}H_{23}N_3O_3$ requiere 305; encontrado 306.2 $(M+H)^+$.

PREPARACION 6

Acido 3-cloro-4-[(1-metiletil)oxi]benzoico



Propan-2-ol (2.45 ml) y PPh_3 (1.18 g) se disolvieron en THF (30

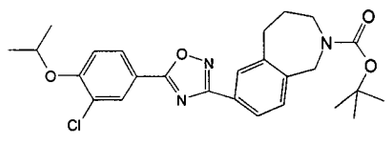
ml), se enfriaron a 0°C, se trataron con 3-cloro-4-hidroxibenzoato de metilo (6.00 g) seguido por la adición gota a gota de DIAD (9.44 ml) y se agitaron a T.A. durante la noche. La mezcla de reacción después se evaporó y se purificó sobre cartuchos de sílice (4 x 100 g), eluyendo con una mezcla de 0 a 40% de EtOAc en pentano para dar el producto crudo (7.00 g) como un aceite incoloro. Esto se disolvió en MeOH (30 ml) y NaOH 2 M acuoso (30 ml) y se agitó a T.A. durante un fin de semana. La mezcla de reacción después se evaporó y se redisolvió en H_2O. Esta solución se lavó con Et_2O, se acidificó a pH = 1 y se extrajo con Et_2O. Estos últimos extractos se secaron sobre $MgSO_4$ anhidro, se filtraron y se evaporaron para dar el compuesto del título (4.16 g) como un sólido blanco.

δH (MeOD, 400MHz): 1.37 (6H, d), 4.77 (1H, heptuplete), 7.12 (1H, d), 7.90 (1H, d), 7.98 (1H, s).

EM (EA): $C_{10}H_{11}{}^{35}ClO_3$ requiere 214; encontrado 215 $(M+H)^+$.

PREPARACION 7

7-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-carboxilato de 1,1-dimetiletilo



Acido 3-cloro-4-[(1-metiletil)oxi]benzoico (preparación 6) (105 mg, 0.491 mmoles), EDC (113 mg, 0.589 mmoles) y HOBT (90 mg, 0.589

2/2

Organización y
Digitalización CSC Ltda

Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD
PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 10-74455

54. **TÍTULO** _____

_____

_____

_____

51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** _____

DOMICILIO _____

74. **APODERADO** _____

22. **BOGOTÁ, D.C.,** _____

(FORMA P-10)

Organización y
Digitalización CSA Ltda

10-74455

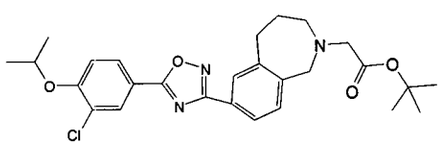
Tomo: 2/2

mmoles) se disolvieron en DMF seca (5 ml) y se agitaron durante 5 minutos. 7-[Hidroxiamino)(imino)metil]-1,3,4,5-tetrahidro-2H-2-benzazepin-2-carboxilato de 1,1-dimetiletilo (preparación 5) (150 mg, 0.491 mmoles) se añadió y la mezcla se agitó durante 1 hora, se calentó a 90°C durante 2 horas después se dejó reposar durante la noche. La reacción se calentó a 90°C durante 3 horas adicionales. EtOAc (50 ml) se añadió y la reacción se lavó con $NaHCO_3$ sat. (ac.) (50 ml) y agua (2x50 ml) antes de secarse sobre $MgSO_4$ anhidro y evaporación del solvente. El aceite crudo obtenido se sometió a cromatografía biotage (1:4 de EtOAc/hexano) para dar 100 mg de un aceite incoloro. El aceite lentamente empezó a solidificarse durante la noche a un sólido blanco ceroso. La trituración con éter/hexano dio el compuesto del título (38 mg) como un sólido blanco después de filtración. Un lote adicional (30 mg) se precipitó de la solución lentamente.

δH (400 MHz, d_6DMSO) 1.31 (9H, s), 1.36 (6H, d), 1.69 (2H, m), 3.06 (2H, m), 3.65 (2H, m), 4.44 (2H, s), 4.84-4.94 (1H, m), 7.38-7.46 (2H, m), 7.84-7.91 (2H, m), 8.11 (1H, dd), 8.18 (1H, d).

PREPARACION 8

[7-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]acetato de 1,1-dimetiletilo

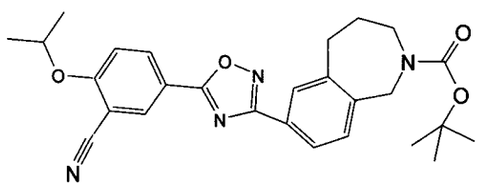


7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1H-2-benzazepina (ejemplo 1) (60 mg, 0.143 mmoles) y carbonato de cesio (140 mg, 0.428 mmoles) se agitaron en DMF seca (5 ml) y se trataron con bromoacetato de ter-butilo (0.032 ml, 0.214 mmoles). La mezcla se agitó a T.A. durante 1.5 horas. EtOAc (50 ml) and éter (20 ml) se añadieron y la mezcla se lavaron con agua (3x 60 ml) y salmuera (40 ml). El secado sobre $MgSO_4$ anhidro y la evaporación de solvente dio un aceite incoloro, claro (80 mg). El aceite se sometió a cromatografía biotage (EtOAc/hexano 3:1) para dar el compuesto del título (65 mg) como un aceite incoloro, claro.

EM (EA) $C_{27}H_{32}{}^{35}ClN_3O_4$ requiere 497; encontrado 498 $(M+H)^+$.

PREPARACION 9

7-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-carboxilato de 1,1-dimetiletilo



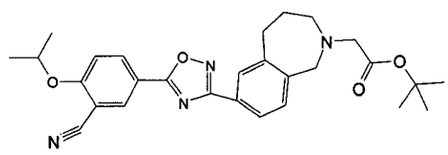
Acido 3-ciano-4-[(1-metiletil)oxi]benzoico (se puede preparar como se describe en WO2005/58848) (302 mg, 1.474 mmoles), EDC (339 mg, 1.768 mmoles) y HOBT (271 mg, 1.768 mmoles) se agitaron en DMF (3 ml) durante 5 minutos. 7-[(Hidroxiamino)(imino)metil]-1,3,4,5-tetrahidro-2H-2-benzazepin-2-carboxilato de 1,1-dimetiletilo (preparación 5) (450 mg, 1.474

mmoles) se añadió y la mezcla de reacción se agitó a T.A. durante 1 hora. Todavía había algo de ácido 3-ciano-4-[(1-metiletil)oxi]benzoico presente. Cantidades adicionales de EDC (100 mg) y 7-[(hidroxiamino)(imino)metil]-1,3,4,5-tetrahidro-2H-2-benzazepin-2-carboxilato de 1,1-dimetiletilo (100 mg) se añadieron y la reacción se agitó durante 1 hora. Después, la reacción se calentó a 80°C durante 3 horas y se dejó reposar durante la noche. La reacción después se calentó a 90°C durante 1 hora. EtOAc (70 ml) se añadió y la mezcla de reacción se lavó con $NaHCO_3$ sat. (50 ml) y agua (2x70 ml), se secó sobre $MgSO_4$ anhidro y se evaporó. El material crudo obtenido se sometió a cromatografía biotage (1:2 de EtOAc/hexano), dando un sólido blanco en la evaporación. La trituración con éter dio el compuesto del título (320 mg) como un sólido blanco.

RMN (400 MHz, d_6DMSO) 1.31 (9H, s), 1.38 (6H, d), 1.69 (2H, br. s), 3.06 (2H, broad s), 3.65 (2H, br. s), 4.44 (2H, s), 4.94-5.03 (1H, m), 7.38-7.43 (1H, m), 7.56 (1H, d), 7.84-7.91 (2H, m), 8.40 (1H, dd), 8.50 (1H, d).

PREPARACION 10

[7-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]acetato de de 1,1-dimetiletilo



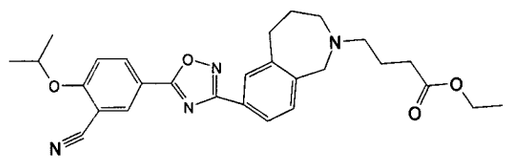
Clorhidrato de 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1H-2-

benzazepin-7-il)-1,2,4-oxadiazol-5-il]benzonitrilo (ejemplo 3) (70 mg, 0.170 mmoles) y carbonato de cesio (167 mg, 0.511 mmoles) en DMF seca (5 ml) se trataron con bromoacetato de ter-butilo (0.038 ml, 0.256 mmoles) y se agitaron a T.A. durante 3 horas para dar un producto individual. EtOAc (40 ml) se añadió y la mezcla se lavó con agua (2X50 ml), se secó sobre $MgSO_4$ anhidro y se evaporó para dar el compuesto del título (85 mg) como un aceite incoloro, claro.

EM (EA) $C_{28}H_{32}N_4O_4$ requiere 488; encontrado 489 $(M+H)^+$.

PREPARACION 11

4-[7-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]butanoato de etilo



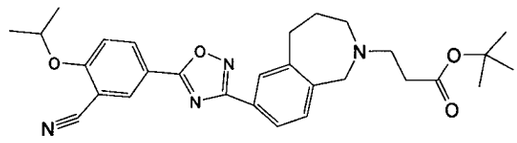
Clorhidrato de 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1H-2-benzazepin-7-il)-1,2,4-oxadiazol-5-il]benzonitrilo (ejemplo 3) (70 mg, 0.170 mmoles) y carbonato de cesio (167 mg, 0.511 mmoles) en DMF seca (5 ml) se trataron con 4-bromobutirato de etilo (0.037 ml, 0.256 mmoles) y se agitaron a 60°C durante 2 horas. Se añadieron cantidades adicionales de 4-bromobutirato de etilo (37 ul) y la reacción se calentó a 60°C durante 3 horas. La reacción se dejó reposar durante la noche. EtOAc (50 ml) se añadió y la mezcla se lavó con agua (2x60 ml), se secó sobre $MgSO_4$ anhidro y se

evaporó para dar el compuesto del título (90 mg) como un aceite incoloro, claro.

EM (EA) $C_{28}H_{32}N_4O_4$ requiere 488; encontrado 489.0 $(M+H)^+$.

PREPARACION 12

3-[7-(5-{3-Ciano-4-[(1-metiletil)oxi] fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]propan-oato de 1,1-dimetiletilo

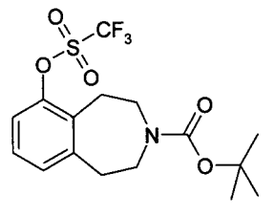


Clorhidrato de 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1H-2-benzazepin-7-il)-1,2,4-oxadiazol-5-il]benzonitrilo (ejemplo 3) (70 mg, 0.170 mmoles) y carbonato de cesio (167 mg, 0.511 mmoles) se agitaron en DMF seca (5 ml) y se trataron con 3-bromopropanoato de 1,1-dimetiletilo (0.043 ml, 0.256 mmoles) después se agitaron a 60°C durante 2 horas. Cantidades adicionales de 3-bromopropanoato de 1,1-dimetiletilo (44 µl) se añadieron y la reacción se agitó a 60°C durante 3 horas. La reacción se dejó reposar durante la noche. Se añadió 3-bromopropanoato de 1,1-dimetiletilo (43 µl) y la mezcla de reacción se agitó a 60°C durante 7 horas, después se dejó reposar durante la noche. EtOAc (50 ml) se añadió y la mezcla de reacción se lavó con agua (2x50 ml), se secó sobre $MgSO_4$ anhidro y se evaporó para dar un aceite incoloro, claro (100 mg). El aceite se solidificó lentamente. La trituración con éter/hexano para dar el compuesto del título (70 mg) como un sólido blanco.

EM (EA) $C_{29}H_{34}N_4O_4$ requiere 502; encontrado 503.0 (M+H).

PREPARACION 13

6-{[(Trifluorometil)sulfonil]oxi}-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo



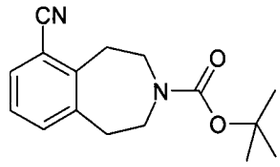
A una solución agitada de 6-hidroxi-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo (se puede preparar como se describe en WO2006/002928) (6.545 g) en DCM seco (100 ml) bajo argón a -10°C se añadió trietilamina (4 ml). Después de 10 minutos, anhídrido trifluorometansulfónico (4.7 ml) se añadió gota a gota durante 10 minutos. La solución incolora se volvió ámbar, después roja. Se dejó que la reacción alcanzara T.A. durante 30 minutos, después se agitó a T.A. durante 18 horas. Después, la reacción se vació en solución saturada de carbonato de sodio (100 ml) y la capa de DCM se recogió, se secó y se evaporó. El compuesto del título (5 g) se obtuvo por cromatografía (eluyendo con DCM).

δH (400 MHz, $CDCl_3$) 7.22-7.12 (3H, m), 3.59-3.57 (4H, m), 3.01-2.99 (4H, m), 1.48 (9H, s);

EM (EA) $C_{16}H_{20}F_3NO_5S$ requiere 395; encontrado 340 $[M+H-56]^+$.

PREPARACION 14

6-Ciano-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo



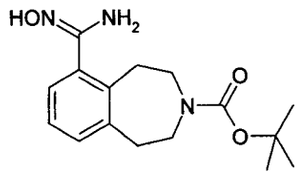
6-{[(Trifluorometil)sulfonil]oxi}-1,2,4,5-tetrahidro-3H-3-benzazepina-3-carboxilato de 1,1-dimetiletilo (preparación 13) (5 g), cianuro de zinc (II) (1.5 g) y tetrakis(trifenilfosfino)paladio(0) (1.5 g) se calentaron en DMF seca a 150°C durante 18 horas. La mezcla de reacción enfriada se diluyó con EtOAc (200 ml) y se filtró. El filtrado se lavó con bicarbonato de sodio saturado, (200 ml), agua (200 ml) y salmuera (200 ml). La mezcla de reacción cruda se secó de la manera usual y se evaporó. La purificación por cromatografía (eluyendo con DCM) dio el compuesto del título (3.4 g).

δH (400 MHz, $CDCl_3$) 7.50 (1H, d), 7.35 (1H, d), 7.27-7.21 (1H, m), 3.62-3.56 (4H, m), 3.22-3.20 (2H, m), 2.97-2.94 (2H, m), 1.47 (9H, s);

EM (EA) $C_{16}H_{20}N_2O_2$ requiere 272; encontrado 217 $[M+H-56]^+$, 273 $[M+H]^+$.

PREPARACION 15

6-[(Hidroxiamino)(imino)metil]-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo



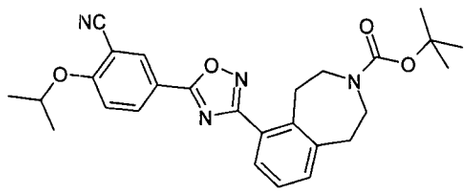
6-Ciano-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo (preparación 14) (1.15 g), clorhidrato de hidroxilamina (1.18 g) y bicarbonato de sodio (1.76 g) se calentaron a 60°C en etanol (100 ml) durante 18 horas bajo argón. La reacción enfriada se evaporó a sequedad, se dividió entre DCM (100 ml) y agua (100 ml). La capa de DCM se recogió y la capa de agua se lavó con DCM (50 ml). Las capas de DCM combinadas se secaron y se evaporaron. El compuesto del título (506 m g) se aisló por cromatografía eluyendo con 5% de metanol en DCM.

δH (400 MHz, $CDCl_3$) 7.27 (1H, s) 7.16-7.13 (2H, m), 5.38 (1H, br. s), 3.58-3.55 (4H, m), 3.05 (2H, br. s), 2.89 (2H, br. s) 1.46 (2H br. s), 1.12 (9H, br. s);

EM (EA) $C_{16}H_{23}N_3O_3$ requiere 305; encontrado 306 $[M+H]^+$.

PREPARACION 16

6-(5-{3-Ciano-4-[(1-metiletil)oxi] fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo



6-[(Hidroxiamino)(imino)metil]-1,2,4,5-tetrahidro-3H-3-benzazepina-3-carboxilato de 1,1-dimetiletilo (preparación 15) (360 mg, 1.179 mmoles) se disolvió en THF (50 ml) y se agitó con hidruro de sodio (60% de dispersión en aceite mineral, 51.9 mg, 1.297 mmoles) bajo argón a temperatura ambiente durante 30 minutos. Después, 3-ciano-4-[(1-metiletil)oxi] benzoato de metilo (se puede preparar como se describe en WO2005058848) (388 mg, 1.768 mmoles) se añadió como una solución en THF (5 ml) y la reacción se calentó a temperatura de reflujo durante 1.5 horas. La reacción enfriada se evaporó y se dividió entre DCM (100 ml) y agua (100 ml). La capa de agua se lavó con DCM (50 ml) y las capas de DCM combinadas se secaron (frita hidrofóbica) y se evaporaron. El producto se aisló por cromatografía de sílice (eluyendo con DCM) para dar 6-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo (505 mg, 1.011 mmoles, 86% de rendimiento) como una espuma blanca.

δH (400 MHz, $CDCl_3$) 8.41 (1H, s), 8.33 (1H, dd), 7.7 (1H, dd),

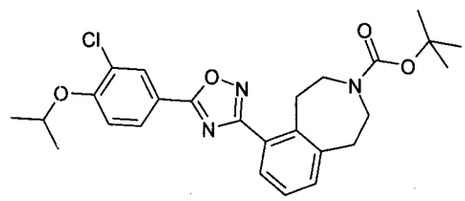
203

7.31-7.25 (2H, m), 7.13 (1H, d), 4.80 (1H, heptuplete), 3.63-3.62 (4H, m), 3.3-3.2 (2H, m), 2.95-3.05 (2H, m), 1.47 (6H, d), 1.43 (9H, br.s);

EM (EA) $C_{27}H_{30}N_4O_4$ requiere 474; encontrado 475 $[M+H]^+$.

PREPARACION 17

6-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo



6-[(Hidroxiamino)(imino)metil]-1,2,4,5-tetrahidro-3H-3-benzazepina-3-carboxilato de 1,1-dimetiletilo (preparación 15) (170 mg, 0.557 mmoles) se disolvió en THF (30 ml) y se agitó con hidruro de sodio (24.49 mg, 0.612 mmoles) bajo argón a temperatura ambiente durante 30 minutos. Después, 3-cloro-4-[(1-metiletil)oxi]benzoato de metilo (se puede preparar como se describe en WO2005058848) (191 mg, 0.835 mmoles) se añadió y la reacción se calentó a temperatura de reflujo durante 1.5 horas. La reacción enfriada se evaporó y se dividió entre DCM (100 ml) y agua (100 ml). La capa de agua se lavó con DCM (50 ml) y las capas de DCM combinadas se secaron (frita hidrofóbica) y se evaporaron. El compuesto del título se aisló por cromatografía de sílice (eluyendo con DCM). 6-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-

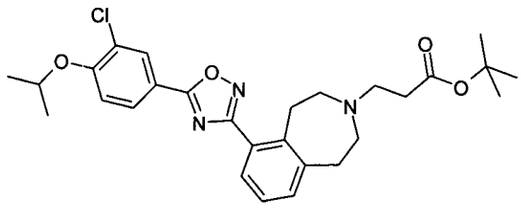
carboxilato de 1,1-dimetiletilo (260 mg, 0.537 mmoles, 96% de rendimiento) se aisló como una espuma blanquecina.

δH (400 MHz, $CDCl_3$) 8.22 (1H, s), 8.05 (1H d), 7.68 (1H, d), 7.30-7.24 (2H, m), 7.06 (1H, d), 4.72 (1H, heptuplete), 3.65-3.55 (4H, m), 3.35-3.25 (2H, m), 2.95-3.05 (2H, m), 1.45 (6H, d), 1.43 (9H, s);

EM (EA) $C_{26}H_{30}{}^{35}ClN_3O_4$ requiere 483; encontrado 484 $[M+H]^+$.

PREPARACION 18

3-[6-(5-{3-Cloro-4-[(1-metiletil)oxi] fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]propanoato de 1,1-dimetiletilo



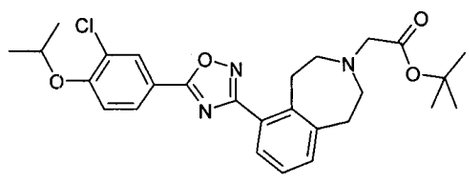
En un recipiente de reacción de microondas de 5 ml se añadió 6-(5-{3-cloro-4-[(1-metil etil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1H-3-benzazepina (base libre del ejemplo 8, obtenida por métodos estándares v.gr., dividiendo entre solventes acuosos orgánicos y básicod y recogiendo el solvente orgánico) (70 mg) en DMF (3 ml) para dar una solución café. Después, carbonato de potasio (101 mg) se añadió seguido por 3-bromopropanoato de 1,1-dimetiletilo (38.1 mg, 0.182 mmoles). La mezcla de reacción se calentó a 100°C durante 10 minutos. La mezcla de reacción enfriada se diluyó con DCM (5 ml) y se purificó por SCX (lavando con metanol

y eluyendo el éster de amino crudo con amoniaco metanólico). La purificación por PADM dio el éster de amino, 3-[6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]propanoato de 1,1-dimetiletilo (25 mg, 0.046 mmoles, 25.4% de rendimiento) aislado como un aceite amarillo claro.

EM (EA) $C_{28}H_{34}{}^{35}ClN_3O_4$ requiere 511; encontrado 512 $[M+H]^+$.

PREPARACION 19

[6-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]acetato de 1,1-dimetiletilo



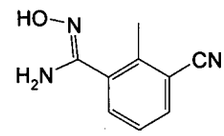
En un recipiente de reacción de microondas de 5 ml se añadió clorhidrato de 6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1H-3-benzazepina (ejemplo 8) (110 mg, 0.262 mmoles). Después, se añadió carbonato de potasio (101 mg) seguido por bromoacetato de 1,1-dimetiletilo (51.0 mg, 0.262 mmoles). La mezcla de reacción se calentó a 100°C durante 10 minutos. La mezcla de reacción enfriada se diluyó con DCM (5 ml) y se purificó por SCX (lavando con metanol y eluyendo el éster de amino crudo con amoniaco metanólico). [6-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]acetato de 1,1-

dimetiletilo (120 mg, 0.241 mmoles, 92% de rendimiento) se aisló como un aceite amarillo pálido.

EM (EA) $C_{27}H_{32}{}^{35}ClN_3O_4$ requiere 497; encontrado 498 $[M+H]^+$.

PREPARACION 20

3-Ciano-N-hidroxi-2-metilbencenocarboximidamida



Una suspensión de 2,6-dicianotolueno (25.0 g, 176 mmoles), clorhidrato de hidroxilamina (73.0 g, 1.06mol) y trietilamina (142 g, 1.41 moles) en cloroformo (500 ml) se agitó a 50°C durante 7 hr, después se dejó reposar a temperatura ambiente durante la noche. La mezcla de reacción se enfrió en hielo, se trató con HCl 5M a pH 1 y se extrajo tres veces con cloroformo. La capa acuosa se extrajo con THF (x 7), se enfrió en hielo, se elevó a pH4 con 40% de NaOH y se extrajo con THF (x 3). Los últimos extractos de THF se combinaron y se evaporaron a sequedad para dar un sólido de color de ante que consistía del producto y aproximadamente un tercio de un equivalente de trietilamina (11.0 g).

^1H RMN (400 MHz, d_4-MeOH) δ (entre otros) 7.70-7.76 (1H, m), 7.57-7.63 (1H, m), 7.35-7.62 (1H, m), 2.58 (3H, s);

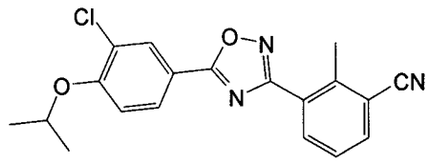
EM (EA) $C_9H_9N_3O$ requiere 175; encontrado 176 $[M+H]^+$.

Los siete extractos formados de THF se combinaron, se

evaporarona sequedad y se disolvieron en agua. La solución acuosa se extrajo dos veces con cloroformo, se ajustó a pH 4 y se extrajo con THF (x 3). La evaporación de los extractos de THF combinados dio 4.5 g adicionales de producto.

PREPARACION 21

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



A una solución de 3-ciano-N-hidroxi-2-metilbencen-carboximidamida (preparación 20) (1.70 g, 9.70 mmoles) en THF (100 ml) se añadió hidruro de sodio (0.427 g, 10.67 mmoles) bajo argón a t.a. y la suspensión se agitó durante 30 min. Después, 3-cloro-4-[(1-metiletil)oxi]benzoato de metilo (se puede preparar como se describe en WO2005058848) (3.33 g, 14.56 mmoles) se añadió y la reacción se calentó a reflujo durante 45 minutos, después se enfrió a T.A. y se agitó durante 3 días.

Por separado, a una suspensión de 3-ciano-N-hidroxi-2-metilbencenocarboximidamida (preparación 20) (10.48 g, 59.8 mmoles) en THF (250 ml) bajo argón a t.a. se añadió hidruro de sodio (2.87 g, 71.8 mmoles) en porciones y la suspensión resultante se agitó a T.A. durante 30

minutos. Se añadió 3-cloro-4-[(1-metiletil)oxi]benzoato de metilo (19.9 g, 87 mmoles) y la reacción se calentó a reflujo durante 4 hr, después se agitó a t.a. durante 16 hr.

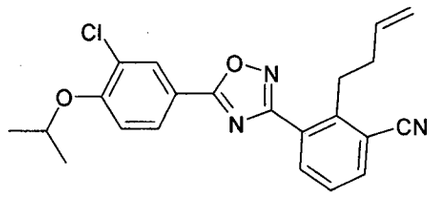
Las dos mezclas de reacción se combinaron. Se añadió agua (200 ml), después la mezcla se extrajo con DCM (2x250 ml). Las capas orgánicas se combinaron, se lavaron con salmuera (100 ml) y se concentraron bajo vacío para dar un sólido blanco crudo (28.1 g). El sólido se redisovió en DCM (200 ml), THF (150 ml) y EtOH (50 ml) y se hizo pasar a través de un tapón corto de sílice (1 cm de profundidad). La elución con DCM seguido por concentración bajo vacío dio un sólido amarillo pálido 3-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2-metilbenzonitrilo (18.10 g, 51.2 mmoles, 80% de rendimiento). La elución de la sílice con DCM-EtOH (2:1) seguido por concentración bajo vacío dio un sólido amarillo pálido 3-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2-metilbenzonitrilo (2.81 g, 6.35 mmoles, 10% de rendimiento). Ambos lotes fueron analíticamente idénticos.

^{1}H RMN (400 MHz, $CDCl_3$) δ 8.27 (1H, d), 8.22 (1H, d), 8.05 (1H, dd), 7.77 (1H, d), 7.45 (1H, t), 7.07 (1H, d), 4.73 (1H, heptuplete), 2.90 (3H, s), 1.47 (6H, d);

EM (EA) $C_{19}H_{16}{}^{35}ClN_3O_2$ requiere 353; encontrado 354 $[M+H]^+$.

PREPARACION 22

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



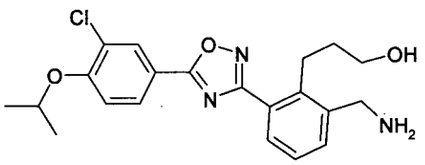
A una solución de diisopropilamina (15.15 ml, 106 mmoles) en THF seco (650 m) a -78°C bajo Ar se añadió ^{n}BuLi (44.3 ml, 70.9 mmoles) hacia abajo por un lado del matraz y la solución resultante se agitó durante 1 hr. Una solución de 3-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2-metilbenzonitrilo (preparación 21) (12.54 g, 35.4 mmoles) en THF seco (100 ml) bajo Ar se añadió gota a gota a ~10 $mlmin^{-1}$, y la solución azul oscuro resultante se agitó a -78°C durante 45 min. Bromuro de alilo (6.13 ml, 70.9 mmoles) se añadió gota a gota a ~3 $mlmin^{-1}$, y la solución rojo oscuro resultante solución se agitó durante 30 min a -78°C. Se añadió HCl(ac.) 1 M (375 ml), la mezcla se dejó calentar a T.A., después las capas se separaron. La capa acuosa se extrajo con EtOAc (2 x 125 ml), después los compuestos orgánicos combinados se lavaron con salmuera (250 ml), se secaron ($MgSO_4$), se filtraron y se concentraron bajo vacío para dar un aceite rojo crudo (12.8 g). Este se redisovió en DCM (20 ml) y se añadió a una columna de sílice pre-humedecida (isohexano) (5 cm x 5 cm). La elución con EtOAc-isohexano (1:3) y la concentración de las fracciones deseadas dio un sólido

anaranjado pálido 2-(3-buten-1-il)-3-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)benzonitrilo (9.50 g, 20.98 mmoles, 59.2% de rendimiento).

^{1}H RMN (400 MHz, $CDCl_3$) δ8.26 (1H, d), 8.24 (1H, d), 8.05 (1H, dd), 7.79 (1H, d), 7.46 (1H, t), 7.07 (1H, d), 5.94 (1H, ddt), 5.07 (1H, dq), 5.01 (1H, dd), 4.73 (1H, heptuplete), 3.40 (2H, t), 2.47 (2H, qd), 1.45 (6H, d); EM (EA) $C_{22}H_{20}{}^{35}ClN_3O_2$ requiere 393; encontrado 394 $[M+H]^+$.

PREPARACION 23

3-[2-(Aminometil)-6-(5-{3-cloro-4-[(1-metiletil)oxi] fenil}-1,2,4-oxadiazol-3-il)fenil]-1-propanol



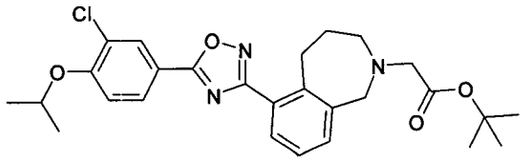
A través de una solución de 2-(3-buten-1-il)-3-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)benzonitrilo (preparación 22) (8.26 g, 20.97 mmoles) en DCM (125 ml) bajo Ar a -78°C se hizo burbujear Ar después O_2 (5 min cada uno). El ozonolizador (modelo 502; 75 lh^{-1}; 0.3 A) se conectó y la solución anaranjada se ozonolizó hasta que se volvió de color verde opaco-gris (3 hr). El ozonolizador se desconectó, y O_2, después Ar se hicieron burbujear a través de la solución (10 min cada uno). La solución se dejó calentar a T.A. bajo Ar, después se concentró bajo vacío para dar un aceite amarillo opaco. Este se redisovió en THF seco (200 ml), se añadió BH_3.DMS

(9.96 ml, 105 mmoles) (CUIDADO: evolución de gas), y la solución se agitó a T.A. durante 18 hr y después a 40°C durante 3 hr. La reacción se enfrió a 0°C, después HC acuosol 0.1M (150 ml) se añadió cuidadosamente (CUIDADO: evolución de gas), después se dejó agitar a T.A. durante 18 hr. La solución se hizo pasar directamente a una columna de SCX-2 (50 g), lavando con MeOH. El producto se eluyó con NH_3 0.5M en MeOH; la concentración bajo vacío dio una espuma anaranjada 3-[2-(aminometil)-6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol -3-il)fenil]-1-propanol (2.73 g, 3.95 mmoles, 18.9% de rendimiento).

^{1}H RMN (400 MHz, $CDCl_3$) δ (entre otros) 8.23 (1H, d), 8.05 (1H, dd), 7.86 (1H, d), 7.46 (1H, d), 7.34 (1H, t), 7.06 (1H, d), 4.72 (1H, heptuplete), 4.03 (2H, s), 3.47 (2H, t), 3.27 (2H, t), 1.78 (2H, quin), 1.45 (6H, d); EM (EA) $C_{21}H_{24}{}^{35}ClN_3O_3$ requiere 401; encontrado 402 $[M+H]^+$.

PREPARACION 24

[6-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2*H*-2-benzazepin-2-il]acetato de 1,1-dimetiletilo



A una solución de 3-[2-(aminometil)-6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)fenil]-1-propanol (preparación 23) (424

mg, 1.055 mmoles) y trifenilfosfina (1384 mg, 5.28 mmoles) en DCM seco (150 ml) a T.A. bajo Ar se añadió DIAD (0.974 ml, 5.01 mmoles) gota a gota durante 2 min y la solución amarillo pálido resultante se agitó a T.A. durante 2 hr. La solución se concentró a ~10 ml, después se hizo pasar un cartucho de SCX-2 (10 g), lavando con MeOH. El producto se eluyó con NH_3 0.5M en MeOH; la concentración bajo vacío dio un aceite anaranjado pálido (>900 mg). La purificación por SCX-2 se repitió para remover óxido de trifenilfosfina restante para dar un aceite amarillo pálido (314 mg). El aceite se redisovió en DCM (40 ml), BOC_2O (0.367 ml, 1.583 mmoles) y DMAP (6.44 mg, 0.053 mmoles) se añadieron secuencialmente y se agitó bajo Ar durante 2 hr. Se añadió NH_4Cl acuoso saturado (20 ml), después la capa acuosa se extrajo con DCM (25 ml). Las capas orgánicas se combinaron, se hicieron pasar a través de una frita hidrofóbica y se concentró bajo vacío para dar un aceite crudo café pálido (496 mg). La cromatografía instantánea (sílice; instantánea 25M; gradiente lineal (0.1-1%) MeOH en DCM) dio un aceite amarillo 6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-carboxilato de 1,1-dimetiletilo (130 mg). Este material se redisovió en HCl 4 M en dioxano (5 ml, 20.00 mmoles) y se agitó a T.A. durante 3 hr. La solución se añadió a una columna SCX-3 (10 g) y se lavó con MeOH. El producto se eluyó con NH_3 0.5 M en MeOH; la concentración bajo vacío dio un sólido blanco pálido (102 mg).El producto se redisovió en DMF seca (3 ml); carbonato de potasio (74.1 mg, 0.536 mmoles) y bromoacetato de ter-butilo (0.042 ml, 0.281 mmoles) se añadieron, después la suspensión se

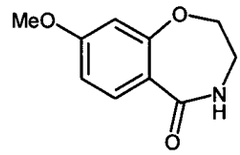
sometió a irradiación a 100°C durante 10 min en el microondas. La mezcla se diluyó con DCM (7 ml), después se añadió a un un cartucho de SCX-3 (10 g) y se lavó con MeOH. El producto se eluyó con NH_3 0.5 M en MeOH; la concentración bajo vacío dio un aceite anaranjado (57 mg). La auto-purificación dirigida a la masa de fase inversa (PADM) dio el producto en una solución de agua-MeCN. Las fracciones deseadas se añadieron a un cartucho de SCX-3 (1 g) y se lavaron con MeOH. El producto se eluyó con NH_3 0.5 M en MeOH; la concentración bajo vacío dio una película clara (21.4 mg) una relación de mezcla de 5:2 de [6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]acetato de 1,1-dimetiletilo y ácido [6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]acético.

Componente mayor: ^{1}H RMN (400 MHz, $CDCl_3$) δ8.22 (1H, d), 8.05 (1H, dd), 7.68 (1H, d), 7.26 (1H, d), 7.25 (1H, t), 7.06 (1H, d), 4.72 (1H, heptuplete), 4.14 (2H, s), 3.28 (2H, br s), 3.23 (2H, t), 3.16 (2H, s), 1.77 (2H, m), 1.47 (9H, s), 1.43 (6H, d);

EM (EA) $C_{27}H_{32}{}^{35}ClN_3O_4$ requiere 497; encontrado 498 $[M+H]^+$.

PREPARACION 25

8-(Metiloxi)-3,4-dihidro-1,4-benzoxazepin-5(2*H*)-ona



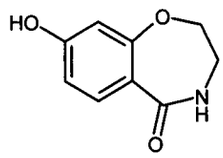
DIAD (32.1 ml, 165 mmoles) se añadió gota a gota durante 15 min a una solución agitada, enfriada con hielo de 2-hidroxi-4-(metiloxi)benzoato de metilo (24.18 g, 150 mmoles), (2-hidroxietil)carbamato de 1,1-dimetiletilo (27.3 g, 150 mmoles) y trifenilfosfina (43.3 g, 165 mmoles) en THF (450 ml) después se agitó y se dejó calentar a temperatura ambiente durante 2 horas. La mezcla de reacción se evaporó para dar 129.9 g de un aceite amarillo viscoso. Se añadió ácido trifluoroacético (60 ml, 779 mmoles) en diclorometano (DCM) (350 ml) y la reacción se dejó a temperatura ambiente durante 65 horas después se evaporó a sequedad. El residuo resultante se disolvió en 500 ml de éter y se extrajo con HCl 2M (200 ml y 2x75 ml). Los extractos de ácido combinados se lavaron con 200 ml de éter después 500 g de hielo se adieron junto con 250 ml de EtOAc y la mezcla se basificó con hidróxido de sodio al 50% de con agitación vigorosa. Los compuestos orgánicos se separaron y la capa acuosa se extrajo adicionalmente con 4x75 ml de EtOAc y los compuestos orgánicos combinados se secaron (sulfato de magnesio) y se evaporaron para dar 21.1 g de un aceite amarillo. El aceite se disolvió en tolueno (350 ml) y se agitó y se sometió a reflujo durante 24 horas después se evaporó y se purificó por

cromatografía instantánea eluyendo con EtOAc para dar el compuesto del título (8.61 g) como un sólido blanco.

EM (EA) $C_{10}H_{11}NO_3$ requiere 193; encontrado 194 $[M+H]^+$.

PREPARACION 26

8-Hidroxi-3,4-dihidro-1,4-benzoxazepin-5(2*H*)-ona

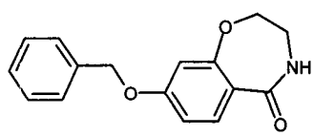


Una mezcla de 8-(metiloxi)-3,4-dihidro-1,4-benzoxazepin-5(2H)-ona (preparación 25) (7.98 g, 41.3 mmoles) y ácido bromhídrico (100 ml, 1842 mmoles) se agitó y se calentó a 110°C durante 7 horas. Después, la mezcla de reacción se evaporó y azeotropó dos veces con 150 ml de etanol para dar el compuesto del título (8.66 g) sólido café claro que se usó sin purificación.

EM (EA) $C_9H_9NO_3$ requiere 179; encontrado 180 $[M+H]^+$.

PREPARACION 27

8-[(Fenilmetil)oxi]-3,4-dihidro-1,4-benzoxazepin-5(2*H*)-ona



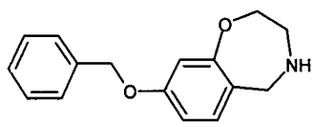
Una mezcla de 8-hidroxi-3,4-dihidro-1,4-benzoxazepin-5(2H)-ona (preparación 26) (8.66 g, 48.3 mmoles), bromuro de bencilo (6.32 ml, 53.2

mmoles) y carbonato de potasio (20.04 g, 145 mmoles) en DMF (80 ml) se agitó y se calentó a 60°C durante 2 horas. La reacción enfriada se diluyó con EtOAc/agua (300 ml cada una) y la capa acuosa se extrajo con EtOAc (2x75 ml). Los compuestos orgánicos combinados se lavaron con 3x100 ml de agua, se secaron (sulfato de magnesio), se evaporaron, se trituraron con éter y se filtraron para dar el compuesto del título (8.39 g) como un sólido blanco.

EM (EA) $C_{16}H_{15}NO_3$ requiere 269; encontrado 270 $[M+H]^+$.

PREPARACION 28

8-[(Fenilmetil)oxi]-2,3,4,5-tetrahidro-1,4-benzoxazepina



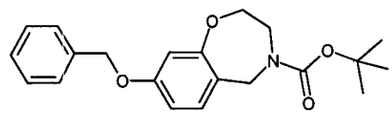
Hidruro de litio-aluminio 1M (62.4 ml, 62.4 mmoles) en THF se añadió bajo argón a una solución agitada de 8-[(fenilmetil)oxi]-3,4-dihidro-1,4-benzoxazepin-5(2H)-ona (preparación 27) (8.39 g, 31.2 mmoles) en THF (150 ml) con enfriamiento con baño de hielo durante 5 minutos. La solución resultante se calentó con agitación a 60°C durante 3 horas. La reacción se enfrió y se extinguió cuidadosamente mediante la adición lenta con enfriamiento con hielo de 150 ml de hidróxido de sodio 2M seguido por 150 ml de EtOAc. Los compuestos orgánicos se separaron y los acuosos se extrajeron con 100 ml de EtOAc. Los extractos orgánicos combinados se secaron (sulfato de magnesio) y se evaporaron para dar el compuesto del

título (7.53 g) como un aceite de color claro.

EM (EA) $C_{16}H_{17}NO_2$ requiere 255; encontrado 256 $[M+H]^+$.

PREPARACION 29

8-[(Fenilmetil)oxi]-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo

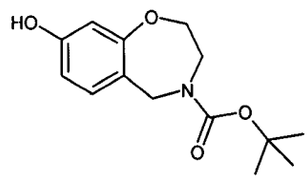


BOC_2O (7.52 ml, 32.4 mmoles) se añadió a una solución de 8-[(fenilmetil)oxi]-2,3,4,5-tetrahidro-1,4-benzoxazepina (preparación 28) (7.52 g, 29.5 mmoles) en DCM (100 ml) y se mantuvo a temperatura ambiente durante 30 minutos. Después, la reacción se evaporó a sequedad y se purificó por cromatografía instantánea eluyendo con 5% de EtOAc en iso-hexano cambiando a 15% de EtOAc en iso-hexano para eluir el producto. Se trituró con iso-hexano y se filtró para dar 7.37 g de sólido blanco.

EM (EA) $C_{21}H_{25}NO_4$ requiere 355; encontrado 300 $[M+H-56]^+$.

PREPARACION 30

8-Hidroxi-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo

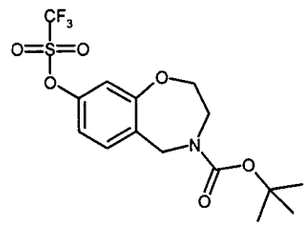


8-[Fenilmetil)oxi]-2,3-dihidro-1,4-benzoxazepina-4(5H)-carboxilato de 1,1-dimetiletilo (preparación 29) (7.35 g, 20.68 mmoles) en una mezcla de THF (40 ml) y EtOH (40 ml) se hidrogenó con 10% de paladio sobre carbón (0.735 g, 6.91 mmoles) durante 18 horas, después se filtró y se evaporó para dar el compuesto del título (5.49 g) como un sólido blanco.

EM (EA) $C_{14}H_{19}NO_4$ requiere 265; encontrado 166 $[M+H-100]^+$.

PREPARACION 31

8-{[(Trifluorometil)sulfonil]oxi}-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo



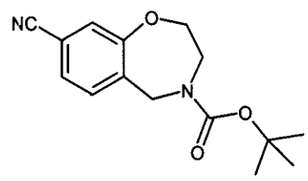
Anhídrido trifluorometansulfónico (0.253 ml, 1.498 mmoles) se añadió a una solución enfriada con hielo de 8-hidroxi-2,3-dihidro-1,4-

benzoxazepina-4(5H)-carboxilato de 1,1-dimetiletilo (preparación 30) (0.265 g, 0.999 mmoles) en piridina (4 ml) y se agitó durante una hora. La mezcla de reacción se evaporó, se disolvió en 40 ml de EtOAc y se lavó con 20 ml de HCl 2M y 20 ml de bicarbonato de sodio saturado, después se secó (sulfato de magnesio) y se evaporó para dar el compuesto del título (399 mg) como una goma amarilla.

EM (EA) $C_{15}H_{18}F_3NO_6S$ requiere 397; encontrado 298 $[M+H-100]^+$.

PREPARACION 32

1,1-Dimetiletil 8-ciano-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato



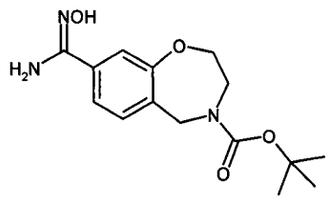
Una mezcla de 8-{[(trifluorometil)sulfonil]oxi}-2,3-dihidro-1,4-benzoxazepina-4(5H)-carboxilatode 1,1-dimetiletilo (preparación 31) (0.397 g, 0.999 mmoles), cianuro de zinc (0.176 g, 1.499 mmoles) y tetrakis(trifenilfosfino)paladio(0) (0.115 g, 0.100 mmoles) en DMF (4 ml) se agitó y se calentó a 80°C durante 2 horas después se enfrió y se diluyó con EtOAc/agua (40 ml cada una) y los compuestos orgánicos se lavaron con 3x20 ml de agua, se secaron (sulfato de magnesio), se evaporaron y se purificaron por cromatografía instantánea eluyendo con 1:4 de EtOAc/iso-

hexano para dar el compuesto del título (198 mg) como una goma que se cristalizó lentamente.

EM (EA) $C_{15}H_{18}N_2O_3$ requiere 274; encontrado 175 $[M+H-100]^+$.

PREPARACION 33

8-[(Hidroxiamino)(imino)metil]-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo

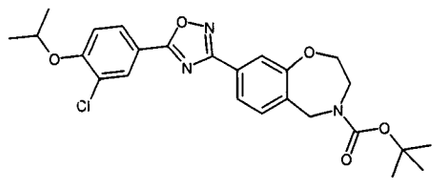


Una mezcla de 8-ciano-2,3-dihidro-1,4-benzoxazepina-4(5H)-carboxilato de 1,1-dimetiletilo (preparación 32) (0.195 g, 0.711 mmoles), clorhidrato de hidroxilamina (0.099 g, 1.422 mmoles) y bicarbonato de sodio (0.299 g, 3.55 mmoles) en etanol (5 ml) se agitó y se calentó a 60°C durante 3 horas. La mezcla de reacción se enfrió, se evaporó y se disolvió en EtOAc/agua (40 ml cada una, se necesito aldgo de calentamiento) y los compuestos orgánicos se secaron (sulfato de magnesio) y se evaporaron para dar el compuesto del título (210 mg) como un sólido blanco.

EM (EA) $C_{15}H_{21}N_3O_4$ requiere 307; encontrado 308 $[M+H]^+$.

PREPARACION 34

8-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo

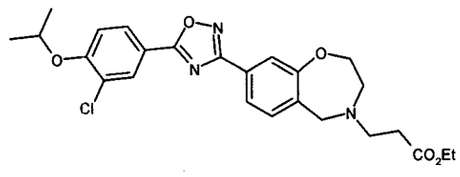


Una mezcla de 8-[(hidroxiamino)(imino)metil]-2,3-dihidro-1,4-benzoxazepina-4(5H)-carboxilato de 1,1-dimetiletilo (preparación 33) (0.195 g, 0.634 mmoles), ácido 3-cloro-4-[(1-metiletil)oxi]benzoico (preparación 6) (0.136 g, 0.634 mmoles), EDC (0.146 g, 0.761 mmoles) y HOBT (0.107 g, 0.698 mmoles) DMF (4 ml) se agitó a temperatura ambiente durante 20 minutos, después se calentó a 100°C durante 17 horas. La mezcla de reacción enfriada se diluyó con EtOAc/agua (40 ml cada una) y los compuestos orgánicos se recogieron, se secaron (sulfato de magnesio), se evaporaron y se purificaron por cromatografía biotage en 1:4 de EtOAc/iso-hexano para dar el compuesto del título (172 mg) como un sólido blanco.

EM (EA) $C_{25}H_{28}{}^{35}ClN_3O_5$ requiere 485; encontrado 486 $[M+H]^+$; $C_{25}H_{28}{}^{37}ClN_3O_5$ requiere 487; encontrado 488 $[M+H]^+$.

PREPARACION 35

3-[8-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]propanoato de etilo

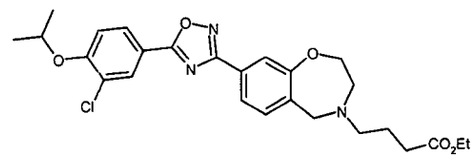


Una mezcla de 8-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1,4-benzoxazepina (ejemplo 13) (0.036 g, 0.199 mmoles), 3-bromopropanoato de etilo (0.084 g, 0.199 mmoles) y DIPEA (0.097 ml, 0.557 mmoles) se agitó y se calentó a 80°C durante 4 horas cuando una porción adicional de 3-bromopropanoato de etilo (0.084 g, 0.199 mmoles) y DIPEA (0.097 ml, 0.557 mmoles) se añadió y se calentó durante la noche cuando una porción adicional de 3-bromopropanoato de etilo (0.084 g, 0.199 mmoles) y DIPEA (0.097 ml, 0.557 mmoles) se añadió y se calentó durante 3 horas más, cuando todo el material de partida se había acabado. La mezcla de reacción enfriada se diluyó con EtOAc/agua (30 ml cada una) y los compuestos orgánicos se secaron (sulfato de magnesio), se evaporaron y se purificaron por cromatografía instantánea eluyendo con 1:1 de EtOAc/iso-hexano para dar el compuesto del título (90 mg) como una goma incolora.

EM (EA) $C_{25}H_{28}{}^{35}ClN_3O_5$ requiere 485; encontrado 486 $[M+H]^+$.

PREPARACION 36

4-[8-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]butanoato de etilo

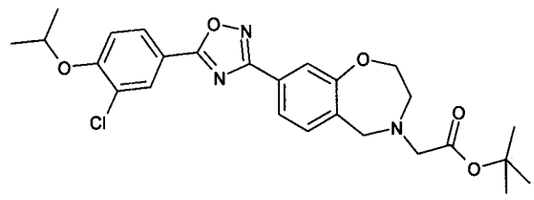


Una mezcla de 8-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1,4-benzoxazepina (ejemplo 13) (0.127 g, 0.3 mmoles), DIPEA (0.052 ml, 0.300 mmoles) y 4-bromobutanoato de etilo (0.059 g, 0.300 mmoles) en acetonitrilo (5 ml) se agitó y se calentó a 70°C durante 15 horas. La mezcla de reacción enfriada se diluyó y se disolvió en EtOAc/agua (30 ml cada una) y los compuestos orgánicos se secaron (sulfato de magnesio), se evaporaron y se purificaron por cromatografía instantánea eluyendo con 1:1 de EtOAc/iso-hexano para dar el compuesto del título (106 mg) como una goma incolora.

EM (EA) $C_{26}H_{30}{}^{35}ClN_3O_5$ requiere 499; encontrado 500 $[M+H]^+$.

PREPARACION 37

[8-(5-{3-Cloro-4-[(1-metiletil)oxi] fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]acetato de 1,1-dimetiletilo

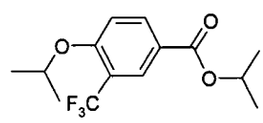


Una mezcla de 8-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1,4-benzoxazepina (ejemplo 13) (0.127 g, 0.301 mmoles), bromoacetato de 1,1-dimetiletilo (0.117 g, 0.601 mmoles) y DIPEA (0.210 ml, 1.203 mmoles) en acetonitrilo (5 ml) se agitó y se calentó a 70°C durante una hora. La mezcla de reacción enfriada se diluyó con EtOAc/agua (30 ml cada una) y los compuestos orgánicos se secaron (sulfato de magnesio), se evaporaron y se purificaron por cromatografía instantánea eluyendo con 1:2 de EtOAc/iso-hexano para dar el compuesto del título (130 mg) como una goma incolora.

EM (EA) $C_{26}H_{30}{}^{35}ClN_3O_5$ requiere 499; encontrado 500 $[M+H]^+$.

PREPARACION 38

4-[(1-Metiletil)oxi]-3-(trifluorometil) benzoato de 1-metiletilo

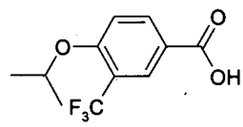


Una mezcla de ácido 4-hidroxi-3-(trifluorometil)benzoico (2.5 g, 12.1 mmoles), 2-yodopropano (2.42 ml, 24.3 mmoles) y carbonato de potasio (3.35 g, 24.3 mmoles) en N,N'-dimetilformamida (200 ml) se calentó a 70°C durante 4 hr. La mezcla de reacción se concentró parcialmente bajo vacío y el residuo se dividió entre EtOAc (150 ml) y agua (150 ml) que contenía algo de hidróxido de sodio acuoso. La fase acuosa se extrajo con EtOAc adicional (2 x 100 ml) y las fracciones orgánicas combinadas se secaron (separador de fase de frita hidrofóbica) y se concentraron bajo vacío para dar el compuesto del título crudo como un aceite amarillo (3.6 g, 12.1 mmoles).

δH (d_6DMSO, 400 MHz): 8.16 (1H, dd), 8.08 (1H, d), 7.43 (1H, d), 5.13 (1H, heptuplete), 4.91 (1H, heptuplete), 1.32 (12H, d).

PREPARACION 39

Acido 4-[(1-metiletil)oxi]-3-(trifluorometil)benzoico



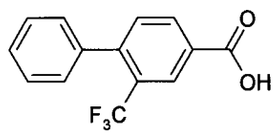
A una mezcla de 4-[(1-metiletil)oxi]-3-(trifluorometil)benzoato de 1-metiletilo (preparación 38) (3.63 g, 12.5 mmoles) en etanol (100 ml) se añadió hidróxido de sodio acuoso (12.5 M, 10.0 ml, 125 mmoles) y la reacción se calentó a reflujo durante 3 hr. La mezcla se concentró bajo vacío y el residuo se dividió entre EtOAc (100 ml) y agua (100 ml) y se acidificó con ácido clorhídrico acuoso. La capa acuosa se extrajo adicionalmente con

EtOAc (100 ml) y las capas orgánicas combinadas se secaron y se concentraron bajo vacío para dar el compuesto del título como un sólido amarillo (2.68 g, 10.8 mmoles).

EM (EA-): $C_{11}H_{11}F_3O_3$ requiere 248; encontrado 247 [M-H$^+$].

PREPARACION 40

Acido 2-(trifluorometil)-4-bifenilcarboxílico



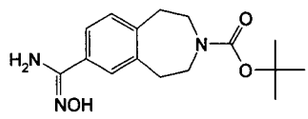
La reacción se dividió en 4, usando un cuarta parte de los reactivos mostrados en cada una: a una mezcla de 4-bromo-3-(trifluorometil)benzonitrilo (4 g, 16.00 mmoles), ácido fenilborónico (3.90 g, 32.0 mmoles) y carbonato de potasio (6.63 g, 48.0 mmoles) en DMF (64 ml) se añadió paladio tetrakistrifenilfosfino(0) (1.849 g, 1.600 mmoles). Cada reacción se calentó en el microondas a 150°C durante 30 minutos. Las mezclas de reacción combinadas se filtraron a través de Celite®, se lavaron con EtOAc y el solvento se removió bajo vacío. El residuo se dividió entre EtOAc (100 ml) y agua (100 ml) y la fase orgánica se lavó con solución de bicarbonato de sodio (100 ml). La fase orgánica se secó ($MgSO_4$), se filtró y el solvente se removió bajo vacío. El aceite café se trituró con DCM y se filtró para dar un sólido amarillo pálido, 2-(trifluorometil)-4-bifenilcarboxamida (2.47 g) que se usó sin purificación adicional. A 2-(trifluorometil)-4-

bifenilcarboxamida (2 g, 7.54 mmoles) en etanol (80 ml) se añadió hidróxido de potasio (4.23 g, 75 mmoles) y agua y la mezcla se calentó a 90°C durante 18 hr. La mezcla de reacción se concentró bajo vacío y el residuo se dividió entre DCM (100 ml) y HCl 2M (100 ml). La fase orgánica se aisló y se secó (separador de fase de frita hidrofóbica) y el solvente se removió bajo vacío para dar el producto crudo. La purificación cromatográfica usó el cartucho de fase inversa, Biotage Horizon, eluyendo 5-100% de MeCN en agua para dar el compuesto del título como un sólido blanquecino (960 mg).

CL-EM (EA-): $C_{14}H_9F_3O_2$ requiere 266; encontrado 265 [M-H$^+$]

PREPARACION 41

7-[(Hidroxiamino)(imino)metil]-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo



Una suspensión de 7-ciano-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo (se puede preparar como se describe en WO2002040471) (5 g, 18.36 mmoles), clorhidrato de hidroxilamina (2.55 g, 36.7 mmoles) y bicarbonato de sodio (7.71 g, 92 mmoles) en etanol (250 ml) se calentó a 50°C durante la noche. Se añadió clorhidrato de hidroxilamina adicional (0.638 g, 9.18 mmoles) a la mezcla de reacción y el calentamiento a 50°C se continuó durante 5 hr. La mezcla de reacción se dejó enfriar y el

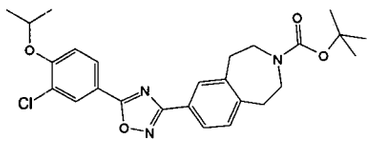
sólido se filtró, la solución se concentró bajo vacío para dar el compuesto del título como un sólido blanco (5.77 g, 17.01 mmoles, 93% de rendimiento).

δH (d_6DMSO, 400 MHz): 9.56 (1H, s), 7.52-7.37 (2H, m), 7.14 (1H, d), 5.77 (2H, br s), 3.50-3.32 (4H, m), 2.91-2.80 (4H, m), 1.41 (9H, s).

EM (EA): $C_{16}H_{23}N_3O_3$ requiere 305; encontrado 306 $[M+H]^+$.

PREPARACION 42

7-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo



A una solución de ácido 3-cloro-4-[(1-metiletil)oxi]benzoico (preparación 6) (1.406 g, 6.55 mmoles) en DMF se añadió HOBT (1.103 g, 7.20 mmoles) y EDC (1.381 g, 7.20 mmoles), la solución resultante se agitó bajo argón durante 10 min a temperatura ambiente. 7-[(Hidroxiamino)(imino)metil]-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo (preparación 41) (2 g, 6.55 mmoles) después se añadió a la mezcla de reacción y la solución se calentó a 80°C durante la noche. El solvente se removió bajo vacío y el residuo se disolvió en metanol para la purificación por cartucho de fase inversa Biotage Horizon, eluyendo 5-100% de acetonitrilo en agua. El producto que contenía fracciones (últimas 5) se concentraron bajo vacío para dar el compuesto del título como un aceite

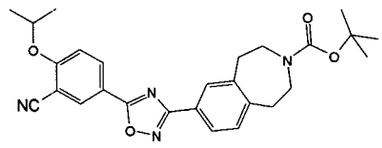
amarillo (950 mg, 1.87 mmoles, 29% de rendimiento).

δH (d_6DMSO, 400 MHz): 8.19 (1H, d), 8.11 (1H, dd), 7.83-7.89 (2H, m), 7.45 (1H, d), 7.37 (1H, d), 4.89 (1H, heptuplete), 3.50 (4H, br.s), 2.96 (4H, br.s), 1.41 (9H, s), 1.36 (6H, d).

EM (EA): $C_{26}H_{30}{}^{35}ClN_3O_4$ requiere 483; encontrado 384 $[M+H-100]^+$.

PREPARACION 43

7-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo



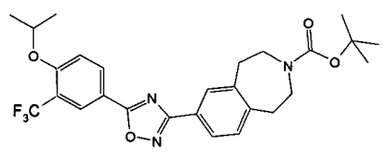
Acido 3-ciano-4-[(1-metiletil)oxi]benzoico (se puede preparar como se describe en WO2005/58848) (687 mg, 3.63 mmoles), HOBT (539 mg, 3.99 mmoles) y EDC (762 mg, 3.99 mmoles) se agitaron en DMF (30 ml) bajo argón durante 20 minutos. 7-[(Hidroxiamino)(imino)metil]-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo (preparación 41) (1.11 g, 3.63 mmoles) se añadió y la mezcla se agitó a temperatura ambiente durante 4 hr antes de calentarse a 80°C durante 20 hr. La mezcla de reacción se dividió entre EtOAc (80 ml) y agua (80 ml) y la capa orgánica se lavó con bicarbonato de sodio acuoso y agua antes de secarse de la manera usual y se evaporó. El residuo se trituró con metanol para dar el compuesto del título

como un sólido blanco (981 mg, 2.07 mmoles).

δH (d_6DMSO, 400 MHz): 8.50 (1H, d), 8.40 (1H, dd), 7.88 (1H, br.s), 7.85 (1H, dd), 7.56 (1H, d), 7.38 (1H, d), 4.98 (1H, heptuplete), 3.53-3.47 (4H, m), 3.00-2.92 (4H, m), 1.41 (9H, s), 1.39 (6H, d).

PREPARACION 44

7-{5-[4-[(1-Metiletil)oxi]-3-(trifluoro-metil)fenil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo



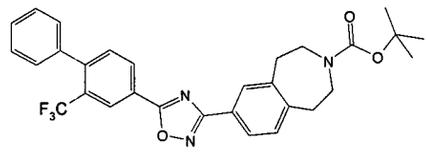
Acido 4-[(1-metiletil)oxi]-3-(trifluorometil)benzoico (preparación 39) (744 mg, 3.00 mmoles), HOBT (446 mg, 3.30 mmoles) y EDC (630 mg, 3.30 mmoles) se agitaron en DMF (28 ml) bajo argón durante 20 minutos. 7-[(Hidroxiamino)(imino)metil]-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo (preparación 41) (915 mg, 3.00 mmoles) se añadió y la mezcla se agitó a temperatura ambiente durante 2 hr antes de calentarse a 80°C durante 20 hr. La mezcla de reacción se dividió entre EtOAc y agua y la capa orgánica se lavó con bicarbonato de sodio acuoso antes de secarse de la manera usual y se evaporó. El residuo se purificó por cartucho de fase inversa Biotage Horizon, eluyendo con 5-100% de acetonitrilo en agua para dar el compuesto del título (749 mg, 1.45 mmoles).

δH (d_6DMSO, 400 MHz): 8.40 (1H, dd), 8.31 (1H, d), 7.89 (1H,

br.s), 7.86 (1H, dd), 7.58 (1H, d), 7.37 (1H, d), 4.98 (1H, heptuplete), 3.54-3.46 (4H, m), 3.00-2.92 (4H, m), 1.41 (9H, s), 1.36 (6H, d).

PREPARACION 45

7-{5-[2-(Trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo



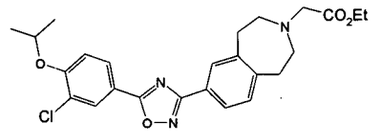
Acido 2-(trifluorometil)-4-bifenilcarboxílico (preparación 40) (284 mg, 1.07 mmoles), HOBT (159 mg, 1.18 mmoles) y EDC (225 mg, 1.18 mmoles) se agitaron en DMF (10 ml) bajo argón durante 20 minutos. 7-[(Hidroxiamino)(imino)metil]-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo (preparación 41) (326 mg, 1.07 mmoles) se añadió y la mezcla se agitó a temperatura ambiente durante 2.5 hr antes de calentarse a 80°C durante 16 hr. La mezcla de reacción se dividió entre EtOAc (30 ml) y agua (30 ml) y la capa orgánica se lavó con bicarbonato de sodio acuoso y agua antes de secarse (separador de fase) y se evaporó. El residuo se trituró con metanol para dar el compuesto del título como un sólido blanco (370 mg, 0.69 mmoles). El filtrado se purificó por cartucho de fase inversa Biotage Horizon, eluyendo con 5-100% de acetonitrilo en agua para dar compuesto del título adicional (70 mg, 0.13 mmoles).

δH (d_6DMSO, 400 MHz): 8.52 (1H, s), 8.50 (1H, d), 7.93 (1H, s),

7.90 (1H, dd), 7.74 (1H, d) 7.56-7.48 (3H, m), 7.41-7.38 (3H, m), 3.55-3.47 (4H, m), 3.02-2.93 (4H, m), 1.41 (9H, s).

PREPARACION 46

[7-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]acetato de etilo

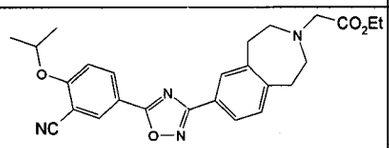
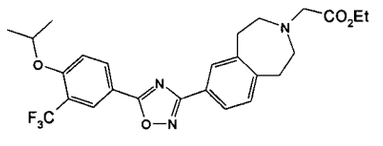
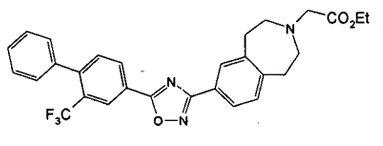


Clorhidrato de 7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1H-3-benzazepina (ejemplo 17) (100 mg, 0.238 mmoles), bromoacetato de etilo (0.043 ml, 0.391 mmoles) y carbonato de cesio (170 mg, 0.521 mmoles) se agitaron a temperatura ambiente en DMF durante 5 horas. La mezcla de reacción se diluyó con éter dietílico (~20 ml) y se lavó con agua (2x ~20 ml), la capa orgánica se hizo pasar a través de un cartucho de separador de fase para secarse y se concentró bajo vacío para dar el compuesto del título (77 mg, 0.16 mmoles, 60% de rendimiento) como un aceite amarillo.

δH (d_6DMSO, 400 MHz): 8.19 (1H, s), 8.11 (1H, dd), 7.81-7.85 (2H, m), 7.45 (1H, d), 7.34 (1H, d), 4.89 (1H, heptuplete), 4.07 (2H, q) 3.42 (2H, s), 3.00-291 (4H, m), 2.77-2.72 (4H, m), 1.36 (6H, d), 1.19 (3H, t).

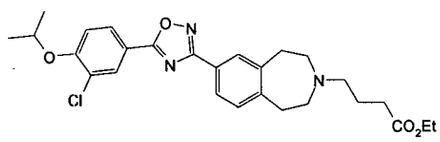
EM (EA): $C_{25}H_{28}{}^{35}ClN_3O_4$ requiere 469; encontrado 470 $[M+H]^+$.

Los siguientes compuestos se hicieron por métodos similares. La preparación 49 se purifcó adicionalmente por PADM.

Prepara-ción	Estructura	Nombre	m/z
47		etil [7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3*H*-3-benzazepin-3-il]acetato	461 $[M+H]^+$
48		etil (7-{5-[4-[(1-metiletil)oxi]-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3*H*-3-benzazepin-3-il)acetato	504 $[M+H]^+$
49		etil (7-{5-[2-(trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3*H*-3-benzazepin-3-il)acetato	522 $[M+H]^+$

PREPARACION 50

4-[7-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3*H*-3-benzazepin-3-il]butanoato de etilo



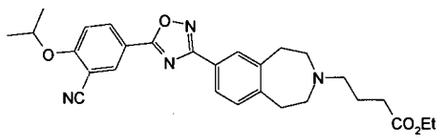
Clorhidrato de 7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1H-3-benzazepina (ejemplo 17) (65 mg, 0.155 mmoles), DIPEA (0.104 ml, 0.593 mmoles) y 4-bromobutanoato de etilo (0.048 ml, 0.339 mmoles) se agitaron a 60°C en DMF (10 ml) durante 24

horas. La mezcla de reacción se dividió entre EtOAc (~30 ml) y agua (~30 ml) y la capa acuosa se extrajo una vez más con EtOAc (~40 ml). Los compuestos orgánicos combinados se concentraron bajo vacío para dar el compuesto del título crudo (100 mg, 0.171 mmoles) como un sólido anaranjado.

EM (EA): $C_{27}H_{32}{}^{35}ClN_3O_4$ requiere 497; encontrado 498 $[M+H]^+$.

PREPARACION 51

4-[7-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3*H*-3-benzazepin-3-il]butanoato de etilo



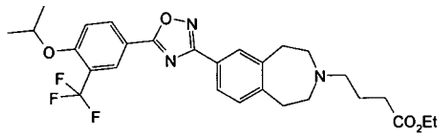
Clorhidrato de 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)-1,2,4-oxadiazol-5-il]benzonitrilo (ejemplo 18) (200 mg, 0.534 mmoles), DIPEA (0.327 ml, 1.869 mmoles) y 4-bromobutanoato de etilo (0.153 ml, 1.068 mmoles) se agitaron a temperatura ambiente en DMF (10 ml) durante 5 horas, la mezcla de reacción después se calentó a 60°C durante 5 hr, la mezcla de reacción se dejó reposar durante la noche a temperatura ambiente, 4-bromobutanoato de etilo adicional (0.076 ml, 0.534 mmoles) se añadió y la mezcla de reacción se calentó a 60°C durante 6 horas. La mezcla de reacción se dividió entre acetato de etilo (~30 ml) y agua (~30 ml) y la capa ac. se extrajo una vez más con acetato de etilo (~40 ml). Los compuestos orgánicos combinados se concentraron bajo vacío para dar el compuesto del

título (218 mg, 0.402 mmoles) como un aceite anaranjado.

EM (EA): $C_{28}H_{32}N_4O_4$ requiere 488; encontrado 489 $[M+H]^+$.

PREPARACION 52

4-(7-{5-[4-[(1-Metiletil)oxi]-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3*H*-3-benzazepin-3-il)butanoato de etilo

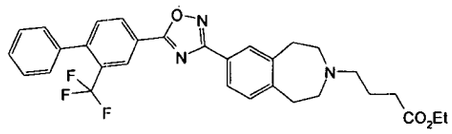


Clorhidrato de 7-{5-[4-[(1-metiletil)oxi]-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-2,3,4,5-tetrahidro-1H-3-benzazepina (ejemplo 19) (160 mg, 0.353 mmoles), DIPEA (0.234 ml, 1.342 mmoles) y 4-bromobutanoato de etilo (0.110 ml, 0.767 mmoles) se agitaron a temperatura ambiente en DMF (10 ml) durante 5 horas. La mezcla de reacción después se calentó a 60°C durante 5 hr, y se dejó reposar durante la noche a temperatura ambiente. 4-Bromobutanoato de etilo adicional (0.055 ml, 0.383 mmoles) se añadió y la mezcla de reacción se calentó a 60°C durante 6 horas. La mezcla de reacción se dividió entre EtOAc (~30 ml) y agua (~30 ml) y la capa acuosa se extrajo una vez más con EtOAc (~40 ml). Los compuestos orgánicos combinados se concentraron bajo vacío para dar el compuesto del título (183 mg, 0.310 mmoles) como un sólido anaranjado.

EM (EA): $C_{28}H_{32}F_3N_3O_4$ requiere 531; encontrado 532 $[M+H]^+$.

PREPARACION 53

4-(7-{5-[2-(Trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3*H*-3-benzazepin-3-il)butanoato de etilo

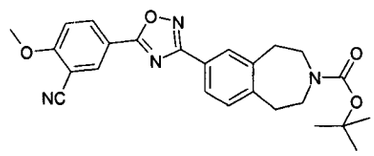


Clorhidrato de 7-{5-[2-(trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-2,3,4,5-tetrahidro-1H-3-benzazepina (ejemplo 20) (200 mg, 0.424 mmoles), DIPEA (0.281 ml, 1.608 mmoles) y 4-bromobutanoato de etilo (0.131 ml, 0.919 mmoles) se agitaron a T.A. en DMF (10 ml) durante 5 horas. La mezcla de reacción después se calentó a 60°C durante 5 hr, y después se dejó reposar durante la noche a temperatura ambiente. 4-Bromobutanoato de etilo adicional (0.066 ml, 0.459 mmoles) se añadió y la mezcla de reacción se calentó a 60°C durante 6 horas. La mezcla de reacción se dividió entre EtOAc (~30 ml) y agua (~30 ml) y la capa acuosa se extrajo una vez más con EtOAc (~40 ml). Los compuestos orgánicos combinados se concentraron bajo vacío para dar el compuesto del título (277 mg, 0.454 mmoles) como un sólido anaranjado.

EM (EA): $C_{31}H_{30}F_3N_3O_3$ requiere 549; encontrado 550 $[M+H]^+$.

PREPARACION 54

7-{5-[3-Ciano-4-(metiloxi)fenil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3*H*-3-benzazepin-3-carboxilato de 1,1-dimetiletilo



7-[(Hidroxiamino)(imino)metil]-1,2,4,5-tetrahidro-3H-3-benzazepina-3-carboxilato de 1,1-dimetiletilo (preparación 41) (240 mg, 0.785 mmoles) se añadió a una suspensión de hidruro de sodio (60% de dispersión en aceite mineral) (23.01 mg, 0.575 mmoles) en THF (5 ml) a temperatura ambiente (nótese efervescencia ligera). La mezcla resultante se agitó a temperatura ambiente durante 30 min, 3-ciano-4-(metiloxi)benzoato de metilo (100 mg, 0.523 mmoles) después se añadió y la mezcla de reacción se calentó a reflujo (75°C) durante 45 min. La mezcla de reacción se diluyó con agua y acetato de etilo y las capas se dividieron, el sólido estaba presente en the mezcla bifásica por lo que se transfirió a un matraz cónico y se agitó a temperatura ambiente durante 2 hr a temperatura ambiente. La mezcla después se dividió y la capa orgánica se concentró bajo vacío, para dar el compuesto del título (280 mg, 0.502 mmoles, 96% de rendimiento) como un aceite amarillo.

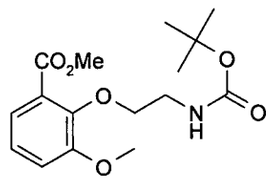
EM (EA): $C_{25}H_{26}N_4O_4$ requiere 447; no estuvo presente el ion de masa.

^{1}H RMN (400 MHz, $CDCl_3$) δ 1H, d (8.44), 1H, dd (8.38), 2H, m

(7.89-7.95), 1H, m (7.35-7.42), 1H, m (7.13-7.17), 3H, s (4.06), 4H, m (3.50-3.66), 4H, m (2.87-3.06), 9H, s (1.50).

PREPARACION 55

2-{[2-({[(1,1-Dimetiletil)oxi]carbonil}amino)etil] oxi}-3-(metiloxi)benzoato de metilo

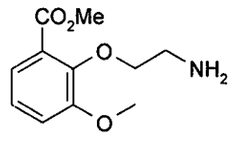


DIAD (23.95 ml, 123 mmoles) se añadió gota a gota a una solución agitada de (2-hidroxietil)carbamato de 1,1-dimetiletilo (18.05 g, 112 mmoles), 2-hidroxi-3-(metiloxi)benzoato de metilo (20.4 g, 112 mmoles) y trifenilfosfina (32.3 g, 123 mmoles) en THF (400 ml) con enfriamiento en un baño de hielo/agua. Se agitó durante 30 min después se evaporó y se usó sin ninguna purificación. LC/EM mostró esencialmente sólo producto y óxido de trifenilfosfina. Rendimiento 98.9 g de material crudo.

EM (EA): $C_{16}H_{23}NO_6$ requiere 325; encontrado 326 $[M+H]^+$.

PREPARACION 56

2-[(2-Aminoetil)oxi]-3-(metiloxi)benzoato de metlo

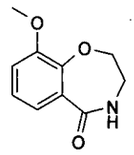


2-{[2-({[(1,1-Dimetiletil)oxi]carbonil}amino)etil]oxi}-3-(metiloxi)-benzoato de metilo (preparación 55) (98.9 g, 304 mmoles) (material crudo, en realidad sólo contenía un máximo de 0.112 moles o 36.4 g) se disolvió en una mezcla de TFA (60 ml, 779 mmoles) y DCM (60 ml) y se dejó a temperatura ambiente durante 1.5 hr. Se evaporó y se disolvió en EtOAc/HCl 2M (250 ml cada una) y los compuestos orgánicos se extrajeron con 2x100 ml de EtOAc adicional. 250 ml de EtOAc se añadió a la fase acuosa y 500 g de hielos se añadieron y la solución se basificó con 50% de hidróxido de sodio. Los compuestos orgánicos se separaron y la fase acuosa se extrajo con 5x75ml de EtOAc adicional. Los compuestos orgánicos combinados se secaron (sulfato de magnesio) y se evaporaron para dar 11.9 g de aceite incoloro. LC/EM mostró 13% de producto y 87% de material ya ciclizado a la benzoxazepina.

EM (EA): $C_{11}H_{15}NO_4$ requiere 225; encontrado 226 $[M+H]^+$.

PREPARACION 57

9-(Metiloxi)-3,4-dihidro-1,4-benzoxazepin-5(2*H*)-ona

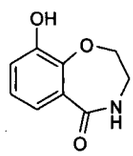


Una solución de 2-[(2-aminoetil)oxi]-3-(metiloxi)benzoato de metilo (preparación 56) (11.9 g, 52.8 mmoles) en tolueno (200 ml) se agitó y se calentó a 110°C durante 1 hora después se enfrió y se evaporó para dar el compuesto del título (10.3 g) como un sólido color arena.

EM (EA): $C_{10}H_{11}NO_3$ requiere 193; encontrado 194 $[M+H]^+$.

PREPARACION 58

9-Hidroxi-3,4-dihidro-1,4-benzoxazepin-5(2*H*)-ona

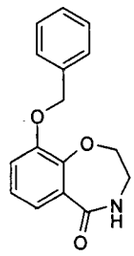


9-(Metiloxi)-3,4-dihidro-1,4-benzoxazepin-5(2H)-ona (preparación 57) (9.3 g, 48.1 mmoles) en ácido bromhídrico (120 ml, 2210 mmoles) se agitó y se calentó a 105°C durante 5 horas. Se evaporó a sequedad, se azeotropó con 200 ml de etanol y se sometió a cromatografía biotage dos veces en 3% de metanol en EtOAc. Se trituró con EtOAc y se filtró para dar 6.61 g de sólido blanco.

EM (EA): $C_9H_9NO_3$ requiere 179; encontrado 180 $[M+H]^+$.

PREPARACION 59

9-[(Fenilmetil)oxi]-3,4-dihidro-1,4-benzoxazepin-5(2H)-ona

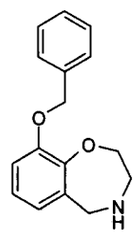


Una mezcla de 9-hidroxi-3,4-dihidro-1,4-benzoxazepin-5(2H)-ona (7.46 g, 41.6 mmoles), bromuro de bencilo (preparación 58) (5.45 ml, 45.8 mmoles) y carbonato de potasio (17.26 g, 125 mmoles) se agitó y se calentó a 60°C en DMF (75 ml) durante 2 horas. Se enfrió, se diluyó con agua (300 ml) y se extrajo con EtOAc (200 ml y 4x75 ml) y los compuestos orgánicos combinados se lavaron con 3x100 ml de agua. Se secaron (sulfato de magnesio), se evaporaron, se trituraron con éter y se filtraron para dar 7.55 g de sólido blanco.

EM (EA): $C_{16}H_{15}NO_3$ requiere 269; encontrado 270 $[M+H]^+$.

PREPARACION 60

9-[(Fenilmetil)oxi]-2,3,4,5-tetrahidro-1,4-benzoxazepina

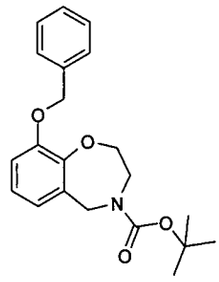


Anhídrido de litio-aluminio 1M (60 ml, 60.0 mmoles) en THF se añadió a una solución agitada de 9-[(fenilmetil)oxi]-3,4-dihidro-1,4-benzoxazepin-5(2H)-ona (preparación 59) (7.4 g, 27.5 mmoles) en THF (150 ml) bajo argón y se calentó a 60°C durante 2 horas, después se enfrió y se extinguió mediante la adición cuidadosa de 100 ml de hidróxido de sodio 2M con enfriamiento con baño de hielo y la suspensión resultante se filtró, el sólidos se lavó con agua y EtOAc y los compuestos orgánicos se secaron (sulfato de magnesio) y se evaporaron para dar 7.01 g de sólido blanco.

EM (EA): $C_{16}H_{17}NO_2$ requiere 255; encontrado 256 $[M+H]^+$.

PREPARACION 61

9-[(Fenilmetil)oxi]-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo



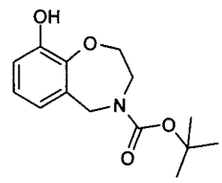
9-[(Fenilmetil)oxi]-2,3,4,5-tetrahidro-1,4-benzoxazepina (preparación 60) (7.01 g, 27.5 mmoles) y BOC_2O (7.01 ml, 30.2 mmoles) se disolvieron en DCM (100 ml) y se dejaron a temperatura ambiente durante una hora, después se evaporaron y se sometieron a cromatografía biotage en 5% de EtOAc en hexano para remover el exceso de BOC_2O y cambiando a 15%

de EtOAc en iso-hexano para eluir el compuesto del título (8.25 g) como un sólido blanco.

EM (EA): $C_{21}H_{25}NO_4$ requiere 355; encontrado 256 $[M+H-100]^+$.

PREPARACION 62

9-Hidroxi-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo

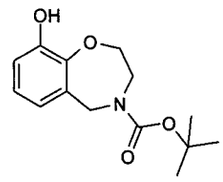


Una solución de 9-[(fenilmetil)oxi]-2,3-dihidro-1,4-benzoxazepina-4(5H)-carboxilato de 1,1-dimetiletilo (preparación 61) (8.25 g, 23.21 mmoles) en etanol (100 ml) se hidrogenó con 10% de paladio sobre carbón (0.825 g, 7.75 mmoles) durante 18 horas, se filtró y se evaporó para dar 6.16 g de sólido blanco.

EM (EA-): $C_{21}H_{25}NO_4$ requiere 265; encontrado 264 $[M-H^+]$.

PREPARACION 62 (Preparación alternativa)

9-Hidroxi-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo

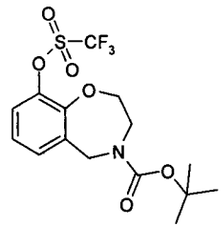


Una suspensión de bromhidrato de 2,3,4,5-tetrahidro-1,4-benzoxazepin-9-ol (preparación 85) (55.7 g, 226 mmoles) en diclorometano (DCM) (550 ml) se trató con trietilamina (47.3 ml, 339 mmoles) y se agitó durante 20 minutos. Esta mezcla se enfrió en hielo/agua a aprox. 5°C y se trató lentamente con una solución de BOC_2O (59.6 ml, 249 mmoles) en diclorometano (DCM) (200 ml) a una velocidad tal para mantener la temperatura interna por debajo de 10°C. Cuando la adición se completó, la mezcla se dejó calentar a temperatura ambiente, se agitó durante 2 horas y se dejó reposar a temperatura ambiente durante la noche. La mezcla se lavó con ácido clorhídrico 0.5M (2x 250 ml) y agua (250 ml), se secó (sulfato de sodio) y se evaporó para dar el compuesto del título como un sólido café pálido (60.5 g).

EM (EA-): $C_{21}H_{25}NO_4$ requiere 265; encontrado 264 $[M-H]^+$.

PREPARACION 63

9-{[(Trifluorometil)sulfonil]oxi}-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo

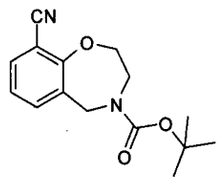


Anhídrido trifluorometansulfónico (6.04 ml, 35.7 mmoles) se añadió a una solución enfriada con hielo de 9-hidroxi-2,3-dihidro-1,4-benzoxazepina-4(5H)-carboxilato de 1,1-dimetiletilo (preparación 62) (6.32 g, 23.82 mmoles) en piridina (100 ml) y se agitó a 0°C durante 2 hr. La piridina se evaporó y el residuo se disolvió en EtOAc. Se lavó con HCl 2M, solución sat. de bicarbonato de sodio, se secó sobre sulfato de magnesio y se evaporó para dar el compuesto del título (9 g) como un aceite amarillo.

EM (EA): $C_{15}H_{18}F_3NO_6S$ requiere 397; encontrado 298 $[M+H-100]^+$.

PREPARACION 64

9-Ciano-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo

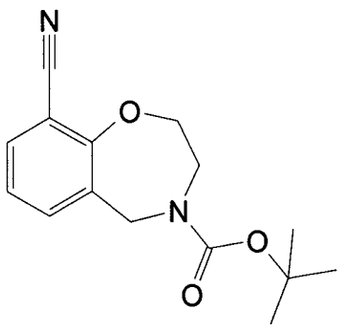


Una solución de 9-{[(trifluorometil)sulfonil]oxi}-2,3-dihidro-1,4-benzoxazepina-4(5H)-carboxilato de 1,1-dimetiletilo (preparación 63) (9 g, 22.65 mmoles), cianuro de zinc (3.99 g, 34.0 mmoles) y tetrakis(trifenilfosfino)paladio(0) (2.62 g, 2.265 mmoles) en DMF (90 ml) se calentó a 80°C durante 24 hr. La reacción se enfrió, se diluyó con EtOAc (400 ml) y agua (400 ml) y se filtró para remover material insoluble. El filtrado se separó y la capa orgánica se lavó con agua, se secó sobre sulfato de magnesio y se evaporó. Se purificó por cromatografía instantánea eluyendo con 1:9 de EtOAc/iso-hexano después 1:3 para dar el compuesto del título (5.1 g) como un aceite incoloro.

EM (EA): $C_{15}H_{18}N_2O_3$ requiere 274; encontrado 174 $[M+H-100]^+$.

PREPARACION 64 (Preparación alternativa)

9-Ciano-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo

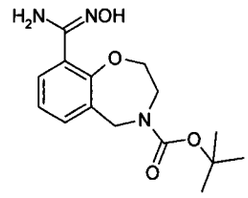


Una solución de 9-bromo-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo (preparación 101) (1.34 g, 4.08 mmoles) en *N,N*-dimetilformamida (11 ml) se desgasificó bajo vacío (3 mm Hg) durante 15 min después se agitó bajo nitrógeno. Se añadieron cianuro de zinc (575 mg, 4.90 mmoles) después tetrakis(trifenilfosfina) paladio(0) (472 mg, 0.41 mmoles) y la mezcla resultante se agitó a 100°C bajo nitrógeno durante la noche, después se diluyó con acetato de etilo. Los residuos insolubles se filtraron y se lavaron con acetato de etilo, se blanquearon durante dos días, se lavaron dos veces con salmuera, se secaron sobre sulfato de magnesio y se concentraron bajo vacío. La purificación del residuo por cromatografía instantánea sobre gel de sílice, eluyendo con 15-45% de acetato de etilo en ciclohexano dio el compuesto del título como un sólido incoloro (980 mg).

EM (EA) $C_{15}H_{18}N_2O_3$ requiere 274 encontrado 275 $[M+H]^+$.

PREPARACION 65

9-[(Hidroxiamino)(imino)metil]-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo

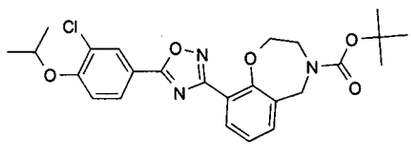


Una suspensión de 9-ciano-2,3-dihidro-1,4-benzoxazepina-4(5H)-carboxilato de 1,1-dimetiletilo (preparación 64) (5.1g, 18.59 mmoles), clorhidrato de hidroxilamina (2.58 g, 37.2 mmoles) y bicarbonato de sodio (7.81 g, 93 mmoles) en etanol (50 ml) se calentó a 60°C durante la noche. Una porción adicional de clorhidrato de hidroxilamina (1 g) se añadió y la reacción se calentó a 60°C durante la noche. El sólido se filtró de la mezcla de reacción y el filtrado se evaporó. El residuo de la evaporación se disolvió en EtOAc, se lavó con agua, se secó sobre sulfato de magnesio y se evaporó. La trituración con éter io el compuesto del título (3.94 g) como un sólido blanco.

EM (EA): $C_{15}H_{21}N_3O_4$ requiere 307; encontrado 308 $[M+H]^+$.

PREPARACION 66

9-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo

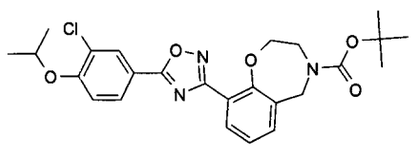


Una solución de 9-[(hidroxiamino)(imino)metil]-2,3-dihidro-1,4-benzoxazepina-4(5H)-carboxilato de 1,1-dimetiletilo (preparación 65) (500 mg, 1.627 mmoles), ácido 3-cloro-4-[(1-metiletil)oxi]benzoico (384 mg, 1.790 mmoles), EDC (468 mg, 2.440 mmoles) y HOBT (299 mg, 1.952 mmoles) en DMF (5 ml) se agitó a T.A. durante la noche después se calentó a 120°C durante 3 hr. La mezcla de reacción se enfrió, se diluyó con EtOAc/agua y los compuestos orgánicos se secaron sobre sulfato de magnesio y se evaporaron. Se purificó por cromatografía instantánea eluyendo con 1:3 de EtOAc/iso-hexano para dar el compuesto del título (320 mg) como un sólido blanco.

EM (EA): $C_{25}H_{28}{}^{35}ClN_3O_5$ requiere 485; encontrado 486 $[M+H]^+$.

PREPARACION 66 (Preparación alternativa)

9-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo

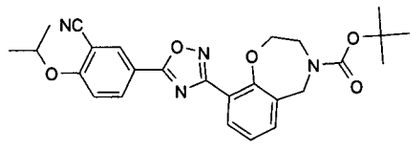


Una mezcla de 9-[(hidroxiamino)(imino)metil]-2,3-dihidro-1,4-benzoxazepina-4(5H)-carboxilato de 1,1-dimetiletilo (preparación 65) (32.9 g, 107 mmoles) y trietilamina (17.9 ml, 128 mmoles) en *N,N*-dimetilformamida seca (DMF) (200 ml) se enfrió en hielo/agua bajo nitrógeno. Una solución de cloruro de 3-cloro-4-[(1-metiletil)oxi]benzoilo (preparación 102) (28.7 g, 123 mmoles) en DMF (100 ml) se añadió durante aprox. 20 minutos. Cuando la adición se completó la mezcla se dejó calentar a temperatura ambiente y se agitó durante 1 hora a temperatura ambiente, después a 120°C durante 3 horas. La mezcla se dejó enfriar y se vació en agua (1 litro). El sólido resultante se extrajo en acetato de etilo (3x 300 ml) y los extractos se combinaron, se lavaron con ácido clorhídrico 1M (2x 250 ml), después solución de carbonato de sodio 1M (3x 250 ml), salmuera (250 ml), se secaron (sulfato de sodio) y se evaporaron. El residuo se purificó por cromatografía sobre sílice. Eluyendo con un gradiente 10-40% de acetato de etilo en isohexano para dar el compuesto del título como un sólido cristalino (42.7 g).

EM (EA): $C_{25}H_{28}{}^{35}ClN_3O_5$ requiere 485; encontrado 486 $[M+H]^+$.

PREPARACION 67

9-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo

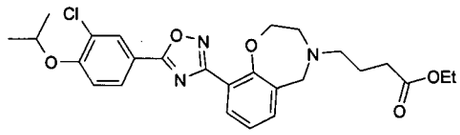


Se preparó de una manera similar a la preparación 66 a partir de la preparación 65.

EM (EA): $C_{26}H_{28}N_4O_5$ requiere 476; encontrado 477 $[M+H]^+$.

PREPARACION 68

4-[9-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]butanoato de etilo



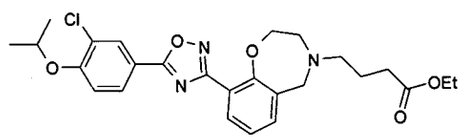
Una solución de clorhidrato de 9-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1,4-benzoxazepina (ejemplo 31) (179 mg, 0.424 mmoles), 4-bromobutanoato de etilo (0.061 ml, 0.424 mmoles) y DIPEA (0.074 ml, 0.424 mmoles) en acetonitrilo (5 ml) se calentó a 70°C durante la noche. 4-Bromobutanoato de etilo adicional (0.061 ml, 0.424 mmoles) y DIPEA (0.074 ml, 0.424 mmoles) se añadieron y la reacción se calentó durante 5 hr adicionales. La reacción enfriada se diluyó

con EtOAc/agua, se separó, los compuestos orgánicos se secaron sobre sulfato de magnesio y se evaporaron. Se purificó por cromatografía instantánea eluyendo con 1:2 de EtOAc/iso-hexano para dar el compuesto del título (135 mg) como un aceite incoloro.

EM (EA): $C_{26}H_{30}{}^{35}ClN_3O_5$ requiere 499; encontrado 500 $[M+H]^+$.

PREPARACION 68 (Preparación alternativa)

4-[9-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]butanoato de etilo



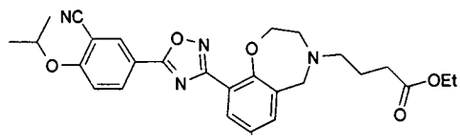
Una mezcla de clorhidrato de 9-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1,4-benzoxazepina (ejemplo 31) (20 g, 47.4 mmoles), carbonato de potasio (16.4 g, 118 mmoles) y yoduro de potasio (7.86 g, 47.4 mmoles) en *N,N*-dimetilformamida (DMF) (250 ml) se trató con 4-bromobutanoato de etilo (7.46 ml, 52.1 mmoles) y la mezcla resultante se agitó a 80°C bajo nitrógeno durante 180 minutos. La mezcla se dejó enfriar y se vació en agua (1000 ml). El precipitado resultante se extrajo en acetato de etilo (3x 250 ml) y los extractos se combinaron, se lavaron con agua (2x 250 ml), después salmuera (150 ml), se secaron (sulfato de sodio) y se evaporaron para dar un aceite viscoso incoloro. El material crudo se purificó por cromatografía sobre sílice, eluyendo con un gradiente de

20-100% de acetato de etilo en isohexano para dar el compuesto del título como un aceite viscoso, incoloro que se cristalizó en reposo (18.3 g).

EM (EA): $C_{26}H_{30}{}^{35}ClN_3O_5$ requiere 499; encontrado 500 $[M+H]^+$.

PREPARACION 69

4-[9-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]butanoato de etilo

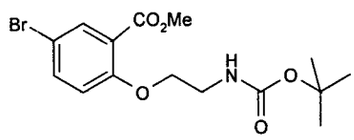


Se preparó de una manera similar a la preparación 68 a partir del ejemplo 32.

EM (EA): $C_{27}H_{30}N_4O_5$ requiere 490; encontrado 491 $[M+H]^+$.

PREPARACION 70

5-Bromo-2-{[2-({[(1,1-dimetiletil)oxi]carbonil} amino)etil]oxi}benzoato de metilo



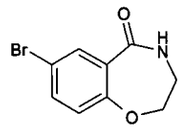
DIAD (9.62 g, 47.6 mmoles) se añadió a una mezcla de 5-bromo-2-hidroxibenzoato de metilo (10 g, 43.3 mmoles), (2-hidroxietil)carbamato de 1,1-dimetiletilo (6.98 g, 43.3 mmoles) y trifenilfosfina

(12.47 g, 47.6 mmoles) en THF (250 ml) y se agitó a T.A. durante 2.5 hr. Trifenilfosfina adicional (2.5 g) se añadió seguido por DIAD (4 ml) y la mezcla se dejó reposar durante la noche. La evaporación y purificación por cromatografía instantánea eluyendo con 25% de EtOAc/hexano dio el compuesto del título como un aceite amarillo (8.92 g).

EM (EA): $C_{15}H_{20}{}^{81}BrNO_5$ requiere 375; encontrado 276 $[M+H-100]^+$.

PREPARACION 71

7-Bromo-3,4-dihidro-1,4-benzoxazepin-5(2*H*)-ona

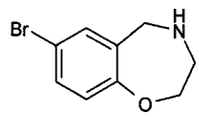


Una solución de 5-bromo-2-{[2-({[(1,1-dimetiletil)oxi]carbonil}amino)etil] oxi}benzoato de metilo (preparación 70) (8.92 g, 23.8 mmmoles) en DCM (18 ml) se trató con TFA (7 ml) y se agitó durante 5 hr. TFA adicional (2 ml) se añadió y la reacción se dejó durante la noche. El solvente se evaporó, se volvió a evaporar con tolueno (5x) y se disolvió en tolueno (50 ml). El residuo resultante se trató con trietilamina (4 equiv) y se calentó a 100°C durante la noche después se evaporó. El residuo se purificó por cromatografía instantánea dos veces eluyendo con 50% de EtOAc/hexano después 40-45% de EtOAc/hexano. Las fracciones se evaporaron para dar el compuesto del título (3.4 g) como un sólido blanco.

EM (EA): $C_9H_8{}^{81}BrNO_2$ requiere 243; encontrado 244 $[M+H]^+$.

PREPARACION 72

7-Bromo-2,3,4,5-tetrahidro-1,4-benzoxazepina

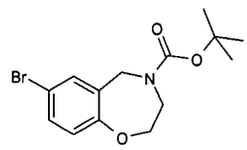


Una solución de 7-bromo-3,4-dihidro-1,4-benzoxazepin-5(2H)-ona (preparación 71) (3.28 g, 13.55 mmoles) en tetrahidrofurano (THF) (30 ml) se agitó bajo argón. Complejo de borano-tetrahidrofurano (81 ml, 81 mmoles) se añadió lentamente y la solución se agitó a T.A. durante 1.5 hr. La solución se calentó a 65°C durante la noche. La reacción se enfrió y MeOH (20 ml) se añadió gota a gota hasta que la efervescencia cesó. Después, HCl 2M (100 ml) se añadió y la reacción se calentó a reflujo durante 1 hora antes de ser enfriada y el solvente se removió por evaporación. La mezcla de reacción se dividió entre EtOAc/Agua y se separó. La capa acuosa se basificó con NaOH 2M, se extrajo con EtOAc, se secó sobre sulfato de magnesio y se evaporó para dar un aceite incoloro (1 g). El sólido precipitado a partir de la capa de EtOAc inicial se filtró y se secó. Este sólido se disolvió en EtOAc/NaOH 2M, se separó y la capa orgánica se secó sobre sulfato de magnesio y se evaporó para dar un aceite incoloro (1.6 g). Los 2 productos se combinaron para dar el compuesto del título (2.6 g) como un aceite incoloro.

EM (EA): $C_9H_{10}{}^{81}BrNO$ requiere 229; encontrado 230 $[M+H]^+$.

PREPARACION 73

7-Bromo-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo

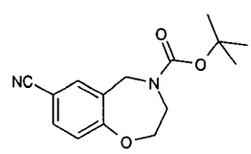


7-Bromo-2,3,4,5-tetrahidro-1,4-benzoxazepina (preparación 72) (2.15 g, 9.43 mmoles) se disolvió en diclorometano (20 ml). Se añadió trietilamina (1.445 ml, 10.37 mmoles) y dicarbonato de bis(1,1-dimetiletilo) (2.263 g, 10.37 mmoles). Se agitó durante 4 horas, después se añadió diclorometano y se lavó con agua (3x20 ml). La mezcla se secó ($MgSO_4$) y se evaporó. Se separó en columna biotage eluyendo con (1:9 de EtOAc/Hexano) y se evaporó para dar el compuesto del título (2.76 g).

EM (EA): $C_{14}H_{18}{}^{81}BrNO_3$ requiere 329; encontrado 230 $[M+H-100]^+$.

PREPARACION 74

7-Ciano-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo



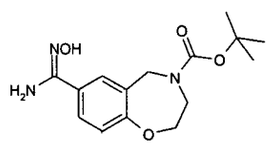
Una mezcla de 7-bromo-2,3-dihidro-1,4-benzoxazepina-4(5H)-

carboxilato de 1,1-dimetiletilo (preparación 73) (2.67g, 8.14 mmoles), cianuro de zinc (1.715 g, 16.27 mmoles) y tetakis(trifenilfosfina)paladio(0) (1.410 g, 1.220 mmoles) en DMF (30 ml) se calentó a 80ºC durante la noche. Tetakis(trifenilfosfina)paladio(0) adicional (700 mg) se añadió y la suspensión amarilla se calentó a 80°C durante 5 hr adicionales. La mezcla de reacción enfriada se diluyó con EtOAc/agua, se separó y los compuestos orgánicos se secaron sobre sulfato de magnesio anhidro y se evaporaron. El crudo se purificó por cromatografía instantánea eluyendo con 1:9 de EtOAc/iso-hexano. Las fracciones combinadas se evaporaron para dar el compuesto del título (2.01 g) como un sólido amarillo.

δH ($CDCl_3$, 400 MHz) : 1.42 (9H, br.s), 3.81 (2H, t), 4.09 (2H, m), 4.43 (1H, s), 4.51 (1H, s), 7.09 (1H, m), 7.47- 7.59 (2H, m).

PREPARACION 75

7-[(Hidroxiamino)(imino)metil]-2,3-dihidro -1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo



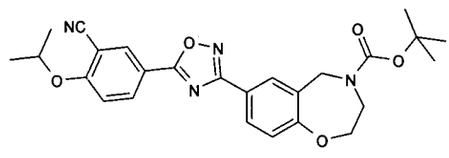
Una suspensión de 7-ciano-2,3-dihidro-1,4-benzoxazepina-4(5H)-carboxilato de 1,1-dimetiletilo (preparación 74) (2.016 g, 7.35 mmoles), clorhidrato de hidroxilamina (1.021 g, 14.70 mmoles) y bicarbonato de sodio (3.09 g, 36.7 mmoles) en etanol (30 ml) se calentó a 60°C durante la noche. El

sólido gris se removió por filtración y el filtrado se evaporó. El residuo resultante se disolvió en EtOAc, se lavó con agua (3x20 ml), se secó ($MgSO_4$) y se evaporó para dar el compuesto del título (1.77 g) como un sólido blanco.

EM (EA): $C_{15}H_{21}N_3O_4$ requiere 307; encontrado 308 $[M+H]^+$.

PREPARACION 76

7-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo



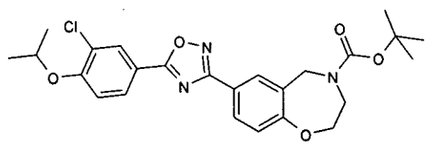
Una solución de 7-[(hidroxiamino)(imino)metil]-2,3-dihidro-1,4-benzoxazepina-4(5H)-carboxilato de 1,1-dimetiletilo (preparación 75) (0.84 g, 2.73 mmoles), ácido 3-ciano-4-[(1-metiletil)oxi]benzoico (se puede preparar como se describe en WO2005/58848) (0.617 g, 3.01 mmoles), EDC (0.786 g, 4.10 mmoles) y HOBT (0.502 g, 3.28 mmoles) en DMF (10 ml) se agitó a T.A. durante la noche. EDC adicional (0.4 g) se añadió y la reacción se agitó durante 3 horas. Después, ácido 3-ciano-4-[(1-metiletil)oxi]benzoico adicional (0.3 g) se añadió, la reacción se calentó a 120°C durante 1 hora y se dejó reposar durante la noche. La mezcla de reacción se dividió entre EtOAc/agua, y la capa orgánica se recogió, se secó ($MgSO_4$) y se evaporó. El crudo resultante se purificó por cromatografía instantánea eluyendo con 20-30% de EtOAc/iso-hexano. El análisis de las fracciones purificadas por CL-EM mostró

que algo del ácido 3-ciano-4-[(1-metiletil)oxi]benzoico estaba presente por lo que se añadió bicarbonato de sodio y EtOAc. La capa de EtOAc se separó, se scó ($MgSO_4$) y se evaporó para dar el compuesto del título (410 mg) como un sólido blanco.

EM (EA): $C_{26}H_{28}N_4O_5$ requiere 476; encontrado 421 $[M+H-56]^+$.

PREPARACION 77

7-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo

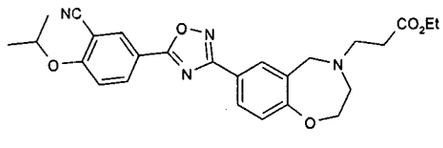


El compuesto del título se preparó por un método similar al de la preparación 76 usando la preparación 75 y el ácido apropiado.

EM (EA): $C_{25}H_{28}{}^{35}ClN_3O_5$ requiere 485; encontrado 430 $[M+H-56]^+$.

PREPARACION 78

3-[7-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]propanoato de etilo

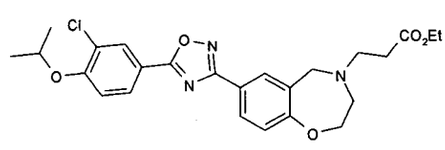


A una solución de clorhidrato d 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1,4-benzoxazepin-7-il)-1,2,4-oxadiazol-5-il]benzonitrilo (ejemplo 35) (0.101 g, 0.268 mmoles) en acetonitrilo (2 ml) se añadió DIPEA (0.094 ml, 0.537 mmoles) y 3-bromopropanoato de etilo (0.051 ml, 0.402 mmoles). La mezcla de reacción se agitó y se calentó a 80°C bajo argón durante 6 horas. DIPEA (0.094 ml, 0.537 mmoles) y 3-bromopropanoato de etilo (0.051 ml, 0.402 mmoles) se añadieron y la reacción se agitó y se calentó a 80°C bajo argón durante la noche. Cantidades adicionales de DIPEA (0.094 ml, 0.537 mmoles) y 3-bromopropanoato de etilo (0.051 ml, 0.402 mmoles) se añadieron y la reacción se calentó nuevamente. La mezcla de reacción se disolvió en EtOAc, se lavó con solución saturada de $NaHCO_3$ (3x15 ml) y agua (15 ml), se secó ($MgSO_4$) y se evaporó. El crudo resultante se purificó por cromatografía instantánea, eluyendo con 10-20% de EtOAc/iso-Hexano (columna Biotage) para dar el compuesto del título (92 mg).

EM (EA): $C_{26}H_{28}N_4O_5$ requiere 476; encontrado 477 $[M+H]^+$.

PREPARACION 79

3-[7-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]propanoato de etilo



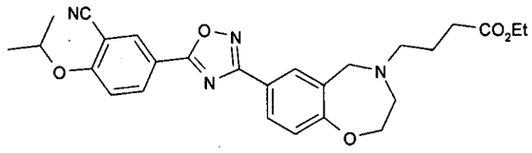
Se preparó por un método similar al de la preparación 78 a partir

del ejemplo 36.

EM (EA): $C_{25}H_{28}{}^{35}ClN_3O_5$ requiere 485; encontrado 486 $[M+H]^+$.

PREPARACION 80

4-[7-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]butanoato de etilo



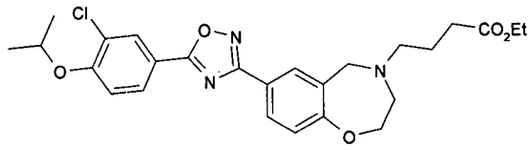
Una solución de clorhidrato de 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1,4-benzoxazepin-7-il)-1,2,4-oxadiazol-5-il]benzonitrilo (ejemplo 35) (0.104 g, 0.276 mmoles) se agitó en acetonitrilo (2 ml). DIPEA (0.097 ml, 0.553 mmoles) y 4-bromobutanoato de etilo (0.059 ml, 0.414 mmoles) se añadieron y la mezcla de reacción se agitó y se calentó a 80°C bajo argón durante 6 horas. 4-Bromobutanoato de etilo adicional (0.059 ml, 0.414 mmoles) y DIPEA (0.097 ml, 0.553 mmoles) se añadieron y la mezcla de reacción se agitó y se calentó a 80°C bajo argón durante la noche. Después, la mezcla de reacción se disolvió en EtOAc, se lavó con solución saturada de $NaHCO_3$ (3x15 ml) y agua (15 ml) y los compuestos orgánicos se secaron ($MgSO_4$) y se evaporaron. El crudo se purificó por cromatografía instantánea, eluyendo con 10-20% de EtOAc/iso-Hexano (columna Biotage) y se evaporó para dar el compuesto del título (84 mg) como un aceite.

EM (EA): $C_{27}H_{30}N_4O_5$ requiere 490; encontrado 491 $[M+H]^+$.

762

PREPARACION 81

4-[7-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]butanoato de etilo

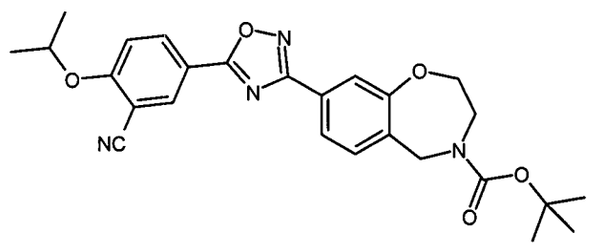


7-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1,4-benzoxazepina (0.105 g, 0.272 mmoles) se agitó en acetonitrilo (2 ml). DIPEA (0.095 ml, 0.544 mmoles) y 4-bromobutanoato de etilo (0.058 ml, 0.408 mmoles) se añadieron y la mezcla de reacción se calentó a 80ºC bajo argón durante 5 horas. DIPEA adicional (0.095 ml, 0.544 mmoles) y 4-bromobutanoato de etilo (0.058 ml, 0.408 mmoles) se añadieron y la mezcla de reacción se calentó a 80°C durante la noche. Después, la mezcla de reacción se disolvió en EtOAc (20 ml), se lavó con $NaHCO_3$ (ac.) (15ml x 3) y con agua (15ml x 3) y los compuestos orgánicos se secaron ($MgSO_4$) y se evaporaron. El crudo se purificó por cromatografía instantánea eluyendo con 20/30% de EtOAc/iso-Hexano (columna Biotage), y se evaporó para dar los compuestos del título como un aceite (80 mg).

EM (EA): $C_{26}H_{30}{}^{35}ClN_3O_5$ requiere 499; encontrado 500 $[M+H]^+$.

PREPARACION 82

8-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo

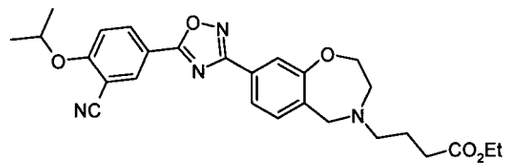


Se preparó a partir de la preparación 33 usando el ácido apropiado, usando el método descrito en la preparación 34.

EM (EA): $C_{26}H_{28}N_4O_5$ requiere 476; encontrado 477 $[M+H]^+$.

PREPARACION 83

4-[8-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]butanoato de etilo

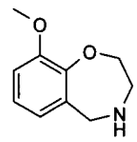


Se preparó a partir del ejemplo 41 usando el método descrito en la preparación 36.

EM (EA): $C_{27}H_{30}N_4O_5$ requiere 490; encontrado 491 $[M+H]^+$.

PREPARACION 84

9-(Metiloxi)-2,3,4,5-tetrahidro-1,4-benzoxazepina

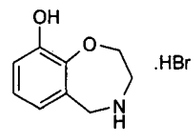


Una solución de 9-(metiloxi)-3,4-dihidro-1,4-benzoxazepin-5(*2H*)-ona (preparación 57) (50 g, 259 mmoles) en tetrahidrofurano seco (THF) (500 ml) se enfrió a aprox. 5°C y se trató lentamente durante aprox. 20 min con hidruro de litio-aluminio 1M en THF (259 ml, 259 mmoles), manteniendo la temperatura interna por abajo de 15°C. Cuando la adición se completó, la mezcla se dejó calentar a temperatura ambiente y se agitó durante 2 horas, después se calentó a reflujo durante 2 horas. La mezcla se dejó enfriar a temperatura ambiente y después se enfrió a aprox. –15°C en un baño de hielo seco/acetona y se trató cuidadosamente con una mezcla 2:1 de THF-agua (100 ml). Cuando la adición se completó la mezcla se trató con más agua (220 ml) y después con hidróxido de sodio 2M hasta que se formó un sólido filtrable. Este se removió por filtración y se lavó con acetato de etilo (500 ml). El filtrado se lavó con salmuera (500 ml) y la fase acuosa se extrajo con acetato de etilo (2x 250 ml). Los extractos orgánicos se combinaron, se secaron (sulfato de sodio) y se evaporaron para dar el compuesto del título como un sólido cristalino blanquecino. (42.9 g)

EM (EA): $C_{10}H_{13}NO_2$ requiere 179; encontrado 180 $[M+H]^+$.

PREPARACION 85

Bromhidrato de 2,3,4,5-tetrahidro-1,4-benzoxazepin-9-ol

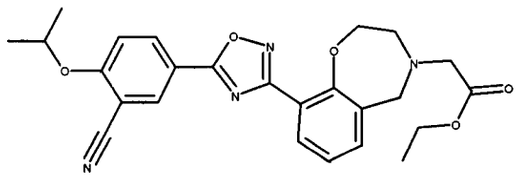


Una suspensión de 9-(metiloxi)-2,3,4,5-tetrahidro-1,4-benzoxazepina (preparación 84) (43.4 g, 242 mmoles) en 33% de HBr en acético ácido (300 ml, 1823 mmoles) se calentó a 80°C durante la noche. La mezcla se dejó enfriar a temperatura ambiente, después se trató con éter dietílico (300 ml) y se agitó durante 30 minutos. El sólido resultante se recogió por filtración, se lavó con éter dietílico (300 ml) y se secó bajo vacío a 40°C para dar el compuesto del título como un polvo café pálido (55.1 g)

EM (EA): $C_9H_{11}NO_2$ requiere 165; encontrado 166 $[M+H]^+$.

PREPARACION 86

[9-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]acetato de etilo



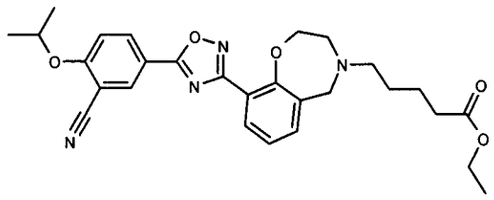
A una solución de 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1,4-benzoxazepin-9-il)-1,2,4-oxadiazol-5-il]benzonitrilo (ejemplo 32) (110 mg,

0.224 mmoles) en acetonitrilo (10 ml) se añadió *N,N*-diisopropiletilamina (0.08 ml, 0.449 mmoles) y bromoacetato de etilo (0.05 ml, 0.449 mmoles). La mezcla de reacción se calentó a 80°C durante 2 horas. La mezcla se dejó enfriar a temperatura ambiente. El solvente se evaporó para dar el compuesto del título como un sólido café (100 mg).

EM (EA) $C_{25}H_{26}N_4O_5$ requiere 462 Encontrado 463 $[M+H]^+$.

PREPARACION 87

5-[9-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]pentanoato de etilo



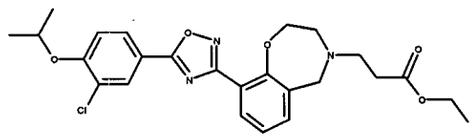
A una solución de 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1,4-benzoxazepin-9-il)-1,2,4-oxadiazol-5-il]benzonitrilo (ejemplo 32) (100 mg, 0.204 mmoles) en acetonitrilo (10 ml) se añadió *N,N*-diisopropiletilamina (0.07 ml, 0.408 mmoles) y 5-bromopentanoato de etilo (0.06 ml, 0.408 mmoles). La mezcla de reacción se calentó a 80°C durante la noche, después se dejó enfriar y el solvente se evaporó. La purificación del residuo por cromatografía instantánea, eluyendo con (40-100% de acetato de etilo en ciclohexano) dio el compuesto del título como un sólido blanquecino (70 mg).

EM (EA) $C_{28}H_{32}N_4O_5$ requiere 504 Encontrado 505 $[M+H]^+$.

267

PREPARACION 88

3-[9-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoato de etilo



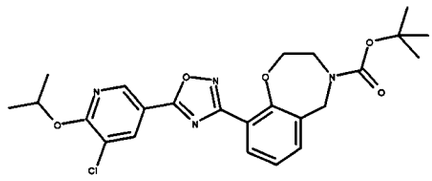
A una solución de clorhidrato de 9-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1,4-benzoxazepina (ejemplo 31) (260 mg, 0.62 mmoles) en acetonitrilo (15 ml) se añadió *N,N*-diisopropiletilamina (0.214 ml, 1.23 mmoles) seguido por 3-bromopropanoato de etilo (0.158 ml, 1.231 mmoles). La mezcla de reacción se calentó a 80°C durante la noche. 1 equiv. de *N,N*-diisopropiletilamina adicional y 3-bromopropanoato de etilo se añadieron y el calentamieno se continuó durante la noche. La mezcla de reacción se enfrió y se evaporó. La purificación del residuo por cromatografía en columna, eluyendo con 50-65% de acetato de etilo en ciclohexano dio el compuesto del título como un aceite amarillo (80 mg).

EM (EA) $C_{25}H_{28}{}^{35}ClN_3O_5$ requiere 485 Encontrado 486 $[M+H]^+$.

268

PREPARACION 89

9-(5-{5-Cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepina-4(5H)-carboxilato de 1,1-dimetiletilo

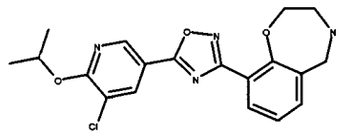


Trietilamina (0.281 ml, 2.02 mmoles) se añadió a una solución agitada de ácido 5-cloro-6-[(1-metiletil)oxi]-3-piridincarboxílico (se puede preparar como se describe en WO9702244; 217 mg, 1.01 mmoles) en *N,N*-dimetilformamida (20 ml) seguido por hidroxibenzotriazol hidratado (185 mg, 1.21 mmoles) después clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (232 mg, 1.21 mmoles) y por último 9-[(hidroxiamino)(imino)metil]-2,3-dihidro-1,4-benzoxazepina-4(5H)-carboxilato de 1,1-dimetiletilo (preparación 65) (310 mg, 1.009 mmoles). La mezcla de reacción se calentó a 60°C durante 48 horas, después se dejó enfriar antes de diluirse con acetato de etilo y lavado con agua. La fase orgánica se secó y se evaporó. La purificación del residuo por cromatografía en columna, eluyendo con 15-25% de acetato de etilo en ciclohexano dio el compuesto del título como una goma color ámbar (280 mg).

EM (EA) $C_{24}H_{27}{}^{35}ClN_4O_5$ requiere 486 encontrado 487 $[M+H]^+$.

PREPARACION 90

Clorhidrato de 9-(5-{5-cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1,4-benzoxazepina

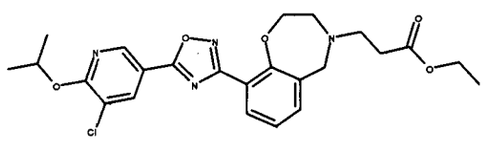


Una mezcla de 9-(5-{5-cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepina-4(5H)-carboxilato de 1,1-dimetiletilo (preparación 89) (190 mg, 0.390 mmoles), cloruro de hidrógeno 4M en dioxano (1 ml, 4.00 mmoles) y 1,4-dioxano (10 ml) se agitó a 60°C durante la noche. La mezcla de reacción se enfrió y un precipitado blanco se formó. El sólido se filtró para dar el producto como un sólido blanco (170 mg).

EM (EA) $C_{19}H_{19}{}^{35}ClN_4O_3$ requiere 386; encontrado 387 $[M+H]^+$.

PREPARACION 91

3-[9-(5-{5-Cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoato de etilo



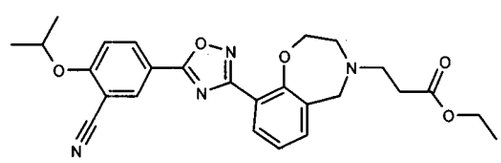
A una solución de clorhidrato de 9-(5-{5-cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1,4-benzoxazepina (preparación 90) (80 mg, 0.189 mmoles) en acetonitrilo (10 ml) se añadió *N,N*-

diisopropiletilamina (0.066 ml, 0.378 mmoles) seguido por 3-bromopropanoato de etilo (0.048 ml, 0.378 mmoles). La mezcla de reacción se calentó a 80°C durante la noche. 1 equivalente adicional de *N,N*-diisopropiletilamina y 3-bromopropanoato de etilo se añadieron y el calentamiento se continuó durante la noche. La mezcla de reacción se enfrió y se evaporó. El residuo se purificó por cromatografía en columna sobre sílice. La elución con 40-60% de acetato de etilo en ciclohexano dio el compuesto del título como un aceite de color verde olivo (28 mg).

EM (EA) $C_{24}H_{27}{}^{35}ClN_4O_5$ requiere 486 Encontrado 487 $[M+H]^+$.

PREPARACION 92

3-[9-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoato de etilo



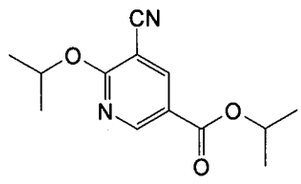
A una solución de clorhidrato de 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1,4-benzoxazepin-9-il)-1,2,4-oxadiazol-5-il]benzonitrilo (ejemplo 32) (90 mg, 0.218 mmoles) en acetonitrilo (10 ml) se añadió *N,N*-diisopropiletilamina (0.076 ml, 0.436 mmoles) seguido por 3-bromopropanoato de etilo (0.056 ml, 0.436 mmoles). La mezcla de reacción se calentó a 80°C durante la noche. 1 equivalente adicional de *N,N*-diisopropiletilamina y 3-bromopropanoato de etilo se añadieron y el calentamiento se continuó durante

la noche. La mezcla de reacción se enfrió y se evaporó. La purificación del residuo por cromatografía en columna sobre sílice, eluyendo con 60-70% de acetato de etilo en ciclohexano dio el compuesto del título como un aceite café (40 mg).

EM (EA) $C_{10}H_{13}NO_2$ requiere 476; encontrado 477 $[M+H]^+$.

PREPARACION 93

5-Ciano-6-[(1-metiletil)oxi]-3-piridincarboxilato de 1-metiletilo



Una mezcla de 5-cloro-6-[(1-metiletil)oxi]-3-piridincarboxilato de 1-metiletilo (se puede preparar como se describe en WO9702244; 7.73 g, 30.0 mmoles) en *N,N*-dimetilformamida seca (DMF) (60 ml) y cianuro de zinc (4.23 g, 36.0 mmoles) a temperatura ambiente se desgasificó y se lavó a chorro con nitrógeno varias veces. Tetrakis(trifenilfosfino)paladio(0) (3.47 g, 3.00 mmoles) se añadió y el procedimiento d desgasificación se repitió. La mezcla de reacción después se calentó a 100°C durante 24 hr. La mezcla de reacción se dejó enfriar a temperatura ambiente, después se filtró para remover residuos sólidos, lavando con un poco de DMF. Una cantidad adicional de cianuro de zinc (4.23 g, 36.0 mmoles) y un lote diferente de tetrakis(trifenilfosfino)paladio(0) (3.47 g, 3.00 mmoles) se añadieron, con la

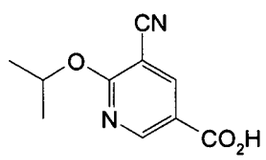
misma desgasificación y lavado a chorro con nitrógeno. El calentamiento se continuó después a 100°C durante 2hr.

La mezcla de reacción se dejó enfriar a temperatura ambiente nuevamente, se diluyó con acetato de etilo y se filtró para remover los residuos sólidos. La solución se concentró a un aceite. En reposo, más sólido se separó. La mezcla se extrajo con acetato de etilo, después la fase orgánica se lavó con agua (2x), salmuera, se secó y se concentró a un aceite anaranjado. El material crudo se cargó en una columna de gel de sílice y se sometió a cromatografía, eluyendo con un gradiente de 0-10% de acetato de etilo en ciclohexano para dar 3.87 g de producto todavía contaminado con trifenilfosfina. Purificación adicional por cromatografía, eluyendo con un gradiente de 0-5% de acetato de etilo en ciclohexano dio el compuesto del título (1.32 g).

EM (EA) $C_{13}H_{16}N_2O_3$ requiere 248; encontrado 248 $[M+H]^+$.

PREPARACION 94

Acido 5-ciano-6-[(1-metiletil)oxi]-3-piridincarboxílico



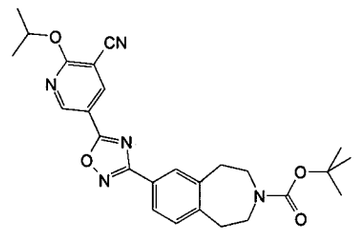
5-Ciano-6-[(1-metiletil)oxi]-3-piridincarboxilato de 1-metiletilo (preparación 93) (1.28 g, 5.15 mmoles) en etanol (20 ml) se trató con hidróxido de sodio (5.15 ml, 10.30 mmoles) y la mezcla se agitó a temperatura

ambiente para dar una solución homogénea, hasta que LC/EM no mostró material de partida. La mezcla se concentró para remover etanol. El residuo se diluyó con agua, después se acidificó con HCl 2M para dar un precipitado blanco espeso. El sólido se filtró, se lavó con agua y se secó durante la noche bajo vacío a 60°C, para dar el compuesto del título (1.07 g),

EM (EA) $C_{10}H_{10}N_2O_3$ requiere 206; encontrado 205 $[M-H]^+$.

PREPARACION 95

7-(5-{5-Ciano-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo



Una solución de ácido 5-ciano-6-[(1-metiletil)oxi]-3-piridincarboxílico (preparación 94) (206 mg, 0.999 mmoles) en diclorometano (5 ml) a temperatura ambiente se trató con cloruro de oxalilo (0.262 ml, 3.00 mmoles) y 1 gota de *N,N*-dimetilformamida (DMF). Después de 1 hr, la solución se concentró para dar el cloruro ácido crudo como una goma amarilla.

7-[(Hidroxiamino)(imino)metil]-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo (preparación 41) (305 mg, 0.999

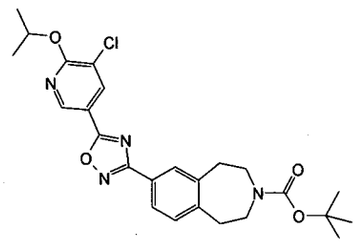
274

mmoles) en DMF (5.00 ml) se trató con trietilamina (0.17 ml, 1.20 mmoles) seguido por el cloruro ácido crudo (descrito antes) en DMF (1 ml). Después de 10 min la mezcla se calentó a 120°C. Después de 2 hr la mezcla de reacción se dejó enfriar a temperatura ambiente y se concentró. El residuo se dividió entre acetato de etilo e hidróxido de sodio diluido. La capa orgánica se lavó con salmuera, se secó y se concentró para dar una goma amarilla, que se cristalizó en reposo. El material crudo se cargó en una columna de gel de sílice y se sometió a cromatografía eluyendo con un gradiente de 0-20% de acetato de etilo en ciclohexano para dar el compuesto del título como un sólido cristalino incoloro (224 mg),

EM (EA) $C_{26}H_{29}N_5O_4$ requiere 475; encontrado 420 $[M+ -tBu]^+$.

PREPARACION 96

7-(5-{5-Cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo



Una suspensión de ácido 5-cloro-6-[(1-metiletil)oxi]-3-piridincarboxílico (se puede preparar como se describe en WO9702244; 215 mg, 0.999 mmoles) en diclorometano (3 ml) a temperatura ambiente se trató

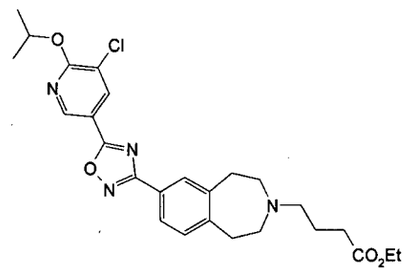
con cloruro de oxalilo (0.26 ml, 3.00 mmoles) y 1 gota de *N,N*-dimetilformamida (DMF). Después de 2 hr, la solución se concentró para dar el cloruro ácido crudo como un aceite amarillo.

7-[(Hidroxiamino)(imino)metil]-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo (preparación 41) (305 mg, 0.999 mmoles) se disolvió en DMF seca (2 ml), se trató con trietilamina (0.17 ml, 1.20 mmoles) y se agitó a temperatura ambiente. Una solución del cloruro ácido crudo (descrito antes) en DMF seca (2 ml) se añadió para dar una solución amarillo pálido, turbia. La mezcla se agitó durante 1.5 hr a temperatura ambiente, después se calentó a 120°C durante 2 hr. La mezcla de reacción se dejó enfriar a temperatura ambiente, y se concentró. El residuo se dividió entre acetato de etilo y agua. La capa orgánica se lavó con agua después salmuera, se secó y se concentró a una espuma color crema. El material crudo se cargó en una columna de gel de sílice y se sometió a cromatografía eluyendo con un gradiente de 0-15% de acetato de etilo en ciclohexano para dar compuesto del título que se obtuvo como una espuma//sólido incoloro, (305 mg),

EM (EA) $C_{25}H_{29}{}^{35}ClN_4O_4$ requiere 484; encontrado 429 [M+ - tBu]$^+$.

PREPARACION 97

4-[7-(5-{5-Cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]butanoato de etilo

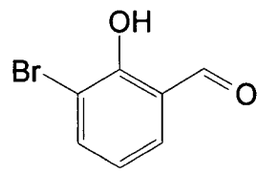


Clorhidrato de 7-(5-{5-cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1H-3-benzazepina (ejemplo 50) (192 mg, 0.499 mmoles) en *N,N*-dimetilformamida (2 ml) a temperatura ambiente se trató con carbonato de potasio (103 mg, 0.748 mmoles) y 4-bromobutanoato de etilo (0.09 ml, 0.60 mmoles). La mezcla se calentó a 100°C. Después de aprox. 2 hr, la mezcla se enfrió y se concentró. El residuo se dividió entre acetato de etilo y agua. La capa de acetato de etilo se lavó con salmuera, se secó y se concentró a una goma incolora. El material crudo se cargó en una columna de gel de sílice y se sometió a cromatografía, eluyendo con un gradiente de 80-100% de acetato de etilo en ciclohexano para dar el compuesto del título como una goma incolora, que se cristalizó lentamente en reposo (185 mg).

EM (EA) $C_{26}H_{31}{}^{35}ClN_4O_4$ requiere 498; encontrado 499 $[M+H]^+$.

PREPARACION 98

3-Bromo-2-hidroxibenzaldehído

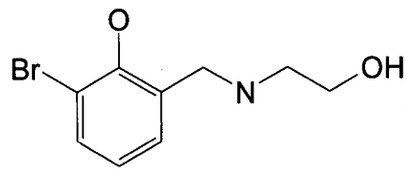


Trietilamina (72 ml, 520 mmoles) se añadió durante 10 minutos a una suspensión de paraformaldehído (23.4 g, 780 mmoles) y dicloruro de magnesio seco (49.5 g, 520 mmoles, Aldrich; CAS 7786-30-3) en THF (1 litro) bajo nitrógeno a temperatura ambiente. La mezcla resultante se agitó durante 20 min, después 2-bromofenol (45 g, 260 mmoles) se añadió durante 5 minutos mediante jeringa. La mezcla resultante se agitó bajo reflujo suavemente durante 6 hr, después se enfrió a temperatura ambiente. La solución se dejó durante el fin de semana y después se diluyó con éter dietílico (500 ml). La fase orgánica se lavó con ácido clorhídrico 2N (500 ml) y las dos fases se separaron. El material insoluble se filtró y la fase orgánica se lavó dos veces con ácido clorhídrico 2N (500 ml) después cinco veces con agua (100 ml), se secó sobre sulfato de magnesio y se concentró bajo vacío para dar el compuesto del título como un sólido incoloro (46.5 g).

EM (EA) $C_7H_5{}^{79}BrO_2$ requiere 200 encontrado 199 $[M-H]^+$.

PREPARACION 99

2-Bromo-6-{[(2-hidroxietil)amino]metil}fenol

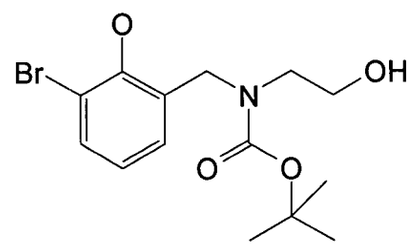


A una solución de 3-bromo-2-hidroxibenzaldehído (preparación 98) (9.6 g, 47.8 mmoles) en tetrahidrofurano (250 ml) a 0°C bajo nitrógeno se añadió 2-aminoetanol (3.02 ml, 50.1 mmoles) después triacetoxiborhidruro de sodio en polvo fino (10.6 g, 50.1 mmoles) y la mezcla resultante se agitó a 0°C durante 1 hr, después se agitó durante la noche y se concentró bajo vacío. El residuo se trituró bajo diclorometano (~200 ml) y el material insoluble se filtró. La fase orgánica se concentró bajo vacío y el residuo se purificó usando una columna SCX para dar el compuesto del título como un sólido blanco (10.1 g).

EM (EA) $C_9H_{10}{}^{79}BrNO_2$ requiere 243 encontrado 244 $[M+H]^+$.

PREPARACION 100

[(3-Bromo-2-hidroxifenil)metil](2-hidroxietil)carbamato de 1,1-dimetiletilo

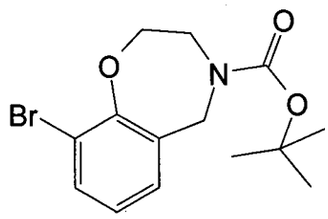


2-Bromo-6-{[(2-hidroxietil)amino]metil}fenol (preparación 99) (2.3 g, 9.35 mmoles) se disolvió en metanol (10 ml) y tetrahidrofurano (40 ml) y la mezcla resultante se enfrió a 0°C. Se añadieron trietilamina (1.95 ml, 14.0 mmoles), después dicarbonato de bis(1,1-dimetiletilo) (2.39 ml, 10.3 mmoles) y la mezcla resultante se agitó a esta temperatura durante 2.5 hr. Trietilamina adicional (195 ml, 1.40 mmoles) y dicarbonato de bis(1,1-dimetiletilo) (239 ml, 1.03 mmoles) se añadieron y la mezcla resultante se dejó calentar a temperatura ambiente y se dejó reposar durante el fin de semana, después se concentró bajo vacío. El residuo se disolvió en acetato de etilo y la fase orgánica se lavó dos veces con ácido clorhídrico 2N, después salmuera y se secó (sulfato de magnesio) y se concentró bajo vacío. La purificación del residuo por cromatografía instantánea sobre gel de sílice, eluyendo con 15-45% de acetato de etilo en ciclohexano dio el compuesto del título como un aceite amarillo pálido (3.4 g).

EM (EA) $C_{14}H_{20}{}^{79}BrNO_4$ requiere 345 encontrado 246 [M+H-$COOC(CH_3)_3$]$^+$.

PREPARACION 101

9-Bromo-2,3-dihidro-1,4-benzoxazepina-4(5*H*)-carboxilato de 1,1-dimetiletilo



Una mezcla de [(3-bromo-2-hidroxifenil)metil](2-hidroxietil)carbamato de 1,1-dimetiletilo (preparación 100) (2.35 g, 6.79 mmoles) y trifenilfosfina (1.96 g, 7.47 mmoles) en tetrahidrofurano (40 ml) bajo nitrógeno se enfrió a 0°C. Azodicarboxilato de diisopropilo (DIAD) (1.47 ml, 7.47 mmoles) se añadió gota a gota y la mezcla resultante se agitó durante 1 hr después se concentró bajo vacío. El solvente se removió y el material se lavó dos veces con salmuera, se secó (sulfato de magnesio), después se concentró bajo vacío. La purificación del residuo por cromatografía instantánea sobre gel de sílice, eluyendo con 5-25% de acetato de etilo en ciclohexano dio el compuesto del título (1.35 g).

EM (EA) $C_{14}H_{18}{}^{79}BrNO_2$ requiere 327 encontrado 228 [M+H-$COOC(CH_3)_3$]$^+$.

Procedimiento alternativo (a partir de 3-bromo-2-hidroxibenzaldehído):

3-Bromo-2-hidroxibenzaldehído (Aldrich; 5.0 g, 24.9 mmoles) en

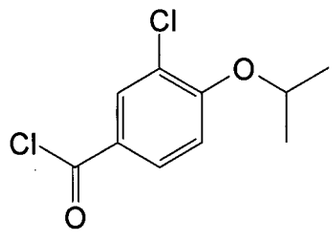
etanol (100 ml) a temperatura ambiente se trató con etanolamina (1.65 ml, 27.4 mmoles) y la mezcla resultante se agitó durante aproximadamente 1 hr. Después, borhidruro de sodio (1.129 g, 29.8 mmoles) se añadió y la mezcla resultante se calentó bajo reflujo durante aproximadamente 2 hr después se enfrió a temperatura ambiente y después se colocó en hielo-agua, se trató con trietilamina (5.2 ml, 37.3 mmoles) seguido por la adición, en porciones, de dicarbonato de bis(1,1-dimetiletilo) (8.14 g, 37.3 mmoles). Una vez que la adición se completó, la mezcla resultante se removió del baño de hielo y la mezcla se agitó a temperatura ambiente durante 30 mins-1 hr. La mezcla resultante se trató con hidróxido de sodio 2M (49.7 ml, 99 mmoles) y se agitó a 50°C durante 1.5 hr, a temperatura ambiente durante la noche, después a 60°C durante 5 hr. Hidróxido de sodio 2M (49.7 ml, 99 mmoles) se añadió y la mezcla resultante se agitó a 60°C durante 2 hr, después a temperatura ambiente durante el fin de semana. La mayoría del etanol se removió bajo vacío y la fase acuosa resultante se acidificó a pH 5 con ácido clorhídrico 2N. La fase acuosa se extrajo tres veces con diclorometano y la fase orgánica se lavó con salmuera, se secó (sulfato de magnesio) y se concentró bajo vacío. El residuo se disolvió en tetrahidrofurano (100 ml) y se trató a temperatura ambiente con trifenilfosfina (10.44 g, 39.8 mmoles) seguido por la adición gota a gota de azodicarboxilato de diisopropilo (DIAD) (7.74 ml, 39.8 mmoles). La mezcla resultante se enfrió brevemente usando hielo-agua y después se agitó durante 1-2 hr a temperatura ambiente, después se concentró bajo vacío. El material crudo en DCM se cargó sobre sílice fina en un embudo

concrecionado, se lavó completamente con ciclohexano (200 ml), seguido por porciones de 3x 500 ml de 10% de EtOAc/ciclohexano. Cada porción se concentró de forma separada. La purificación del residuo por cromatografía instantánea sobre gel de sílice, eluyendo con 0-10% de acetato de etilo en ciclohexano dio el compuesto del título (6.62 g).

EM (EA) $C_{14}H_{18}{}^{79}BrNO_2$ requiere 327 encontrado 228 $[M+H-COOC(CH_3)_3]^+$.

PREPARACION 102

Cloruro de 3-cloro-4-[(1-metiletil)oxi]benzoilo

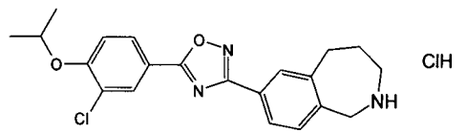


Un matraz de fondo redondo se cargó con ácido 3-cloro-4-[(1-metiletil)oxi]benzoico (disponible de Paragos Product List, 10.2 g, 47.5 mmoles), diclorometano (158 ml) y cloruro de oxalilo (8.29 ml, 95 mmoles). La mezcla de reacción se enfrió a 0°C en un baño de hielo/agua antes de la adición de *N,N*-dimetilformamida (0.158 ml). La solución se dejó calentar a temperatura ambiente durante la noche. El solvente se evaporó para dar el compuesto del título como un sólido color crema (11.4 g).

δH (CDCl3, 400MHz): 1.44 (6H, d), 4.73 (1H, heptuplete), 6.98 (1H, d), 8.0 (1H, dd), 7.98 (1H, d).

EJEMPLO 1

Clorhidrato de 7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1H-2-benzazepina



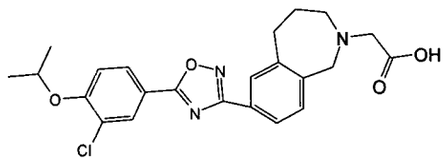
7-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-carboxilato de 1,1-dimetiletilo (preparación 7) (75 mg, 0.155 mmoles) se trató con HCl 4N en dioxano (1162 µl, 4.65 mmoles) y la solución clara se dejó reposar durante 1.5 horas. Un precipitado blanco se formó. Se añadió éter (1 ml) y el sólido blanco se filtró, lavando con éter. El compuesto del título se obtuvo al secar el sólido (45 mg).

δH (400 MHz, d_6DMSO) 1.36 (6H, d), 1.91-1.98 (2H, m), 3.11-3.14 (2H, m), 3.36-3.39 (2H, m), 4.41 (2H, s), 4.85-4.94 (1H, m), 7.46 (1H, d), 7.64 (1H, d), 7.95-7.80 (2H, m), 8.11 (1H, dd), 8.19 (1H, d), 9.04 (2H, banda ancha s);

EM (EA) $C_{21}H_{22}{}^{35}ClN_3O_2$ requiere 383; encontrado 384.0 $[M+H]^+$.

EJEMPLO 2

Acido [7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]acético



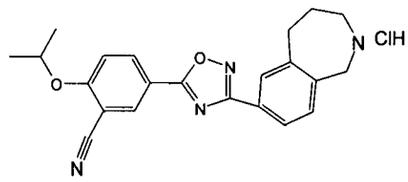
[7-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]acetato d 1,1-dimetiletilo (preparación 8) (65 mg, 0.131 mmoles) se trató con HCl (1305 µl, 5.22 mmoles) (4N en dioxano) y se dejó reposar durante 2 horas. Después, la mezcla de reacción se calentó a 50°C durante 1 hora, después se calentó a 60°C durante 1.25 horas adicionales, antes de la remoción del solvente por evaporación. La trituración con éter/EtOAc falló y el material obtenido se purificó por PADM. Se obtuvo un sólido blanco (20 mg) secando por congelamiento fracciones de PADM apropiadas. Además, el secado bajo vacío a 70°C durante 16 horas dio el compuesto del título (16 mg) como un sólido.

δH (400 MHz, d_6DMSO) 1.36 (6H, d), 1.51-1.53 (2H, m), 2.98-3.00 (2H, m), 3.4 (2H, br.s), 4.10 (2H, s), 4.86-4.92 (1H, m), 7.32 (1H, d), 7.44 (1H, d), 7.83-7.88 (2H, m), 8.11 (1H, dd), 8.18 (1H, d);

EM (EA) $C_{23}H_{24}{}^{35}ClN_3O_4$ requiere 441; encontrado 442 $[M+H]^+$.

EJEMPLO 3

Clorhidrato de 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1H-2-benzazepin-7-il)-1,2,4-oxadiazol-5-il]benzonitrilo



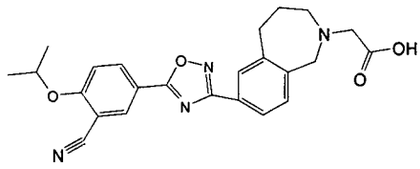
7-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-carboxilato de 1,1-dimetiletilo (preparación 9) (310 mg, 0.653 mmoles) se trató con HCl (3266 µl, 13.06 mmoles) (4N en dioxano) y se agitó. Después de 30 minutos, se formó un precipitado blanco. Después de 1 hora se añadió éter (2 ml) y el precipitado se filtró y se lavó con éter. El compuesto del título (230 mg) se obtuvo al secarse.

δH (400 MHz, d_6DMSO) 1.39 (6H, d), 1.91 (2H, m), 3.11-3.13 (2H, m), 3.37-3.40 (2H, m), 4.42 (2H, s), 4.94-5.02 (1H, m), 7.57 (1H, d), 7.64 (1H, d), 7.96-8.00 (2H, m), 8.41 (1H, dd), 8.52 (1H, d), 9.04 (2H, ancho s);

EM (EA) $C_{22}H_{22}N_4O_2$ requiere 374; encontrado 375.0 $[M+H]^+$.

EJEMPLO 4

Acido [7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]acético



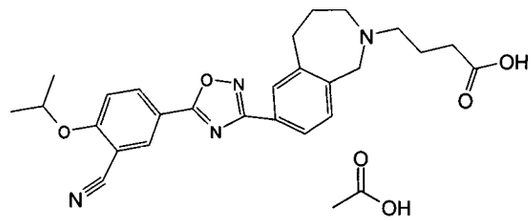
[7-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]acetato de 1,1-dimetiletilo (preparación 10) (85 mg, 0.174 mmoles) se trató con HCl (1305 µl, 5.22 mmoles) (solución 4N en dioxano) y se calentó a 50°C durante 2 horas. Un producto cristalino blanco se formó. La reacción se enfrió a T.A. y el sólido se filtró y se lavó con éter. Al secarse, se obtuvo el compuesto del título (65 mg) como un sólido blanco.

δH (400 MHz, d_6DMSO) 1.39 (6H, d), 1.91-2.00 (2H, m), 3.11-3.12 (2H, m), 3.59 (2H, m), 4.00 (2H, s), 4.60 (2H, s), 4.94-5.02 (1H, m), 7.53-7.59 (2H, m), 7.99-8.06 (2H, m), 8.41 (1H, dd), 8.52 (1H, d);

EM (EA) $C_{24}H_{24}N_4O_4$ requiere 432; encontrado 433 $[M+H]^+$.

EJEMPLO 5

Acetato de ácido 4-[7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]butanoico



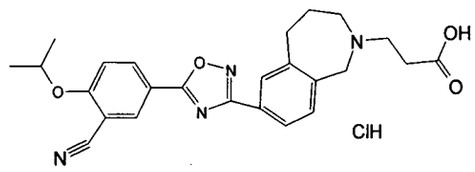
4-[7-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]butanoato de etilo (preparación 11) (90 mg, 0.184 mmoles) disuelto en etanol (20 ml) se trató con solución de hidróxido de sodio (0.184 ml, 0.368 mmoles) (2N (ac.)) seguido por agua (5.00 ml). Esta mezcla se agitó a T.A. durante 3 horas y se dejó reposar durante la noche. Se añadió NaOH 2N (ac.) (150 µl) y la mezcla de reacción se agitó durante 3 horas. Después, etanol se removió por evaporación y la capa acuosa se acidificó usando AcOH. El producto se extrajo en EtOAc (50 ml) y se secó sobre $MgSO_4$. El solvente se removió por evaporación dando un precipitado blanco. Se añadió éter y el sólido se filtró y se lavó con éter para dar el compuesto del título (44 mg) al secarse.

δH (400 MHz, d_6DMSO) 1.39 (6H, d), 1.91-1.95 (4H, m), 2.30 (2H, t), 2.96 (2H, m), 3.13 (2H, m), 3.53 (2H, m), 4.60 (2H, s), 4.94-5.03 (1H, m), 7.57 (1H, d), 7.68 (1H, d), 7.97-8.00 (2H, m), 8.41 (1H, dd), 8.52 (1H, d) 10.6 (1H, v. ancho s), 12.3 (1H, v. ancho s);

EM (EA) $C_{26}H_{28}N_4O_4$ requiere 460; encontrado 461.0 $[M+H]^+$.

EJEMPLO 6

Clorhidrato de ácido 3-[7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]propanoico



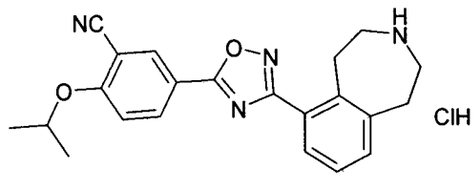
3-[7-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]propanoato de 1,1-dimetiletilo (preparación 12) (70 mg, 0.139 mmoles) se trató con HCl (1045 µl, 4.18 mmoles) (4N en dioxano) y se calentó a 50°C durante 1.5 horas. Un precipitado blanco empezó a formarse. Se añadió éter (0.5 ml) y el sólido blanco se filtró y se lavó con éter para dar el compuesto del título (57 mg) al secrase.

δH (400 MHz, d_6DMSO) 1.39 (6H, d), 1.91-1.96 (2H, m), 2.82 (2H, m), 3.12-3.21 (4H, m), 3.56 (2H, m), 4.62 (2H, s), 4.96-5.02 (1H, m), 7.57 (1H, d), 7.71 (1H, d), 7.99-8.01 (2H, m), 8.41 (1H, dd), 8.52 (1H, d), 10.3 (1H, v. ancho s), 12.8 (1H, v. ancho s);

EM (EA) $C_{25}H_{26}N_4O_4$ requiere 446; encontrado 447.0 $[M+H]^+$.

EJEMPLO 7

Clorhidrato de de 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1H-3-benzazepin-6-il)-1,2,4-oxadiazol-5-il]benzonitrilo



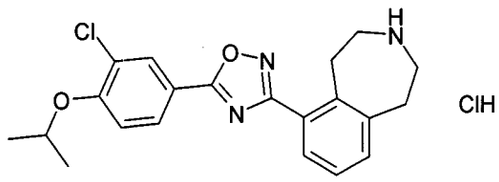
6-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo (preparación 16) (505 mg, 1.064 mmoles) se disolvió en DCM (40 ml) y se trató con ácido trifluoroacético (4 ml, 51.9 mmoles). La mezcla resultante se calentó a reflujo durante 1 hora después se evaporó. El residuo resultante se dividió entre DCM (20 ml) y NaOH 2N (20 ml). La capa de DCM se recogió, se secó (frita hidrofóbica) y se evaporó. La base libre se disolvió en HCl 4M en dioxano y se evaporó para dar la sal de HCl, clorhidrato de 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1H-3-benzazepin-6-il)-1,2,4-oxadiazol-5-il]benzonitrilo (438 mg, 1.066 mmoles, 100% de rendimiento) como un polvo blanquecino.

δH (400 MHz, $CDCl_3$) 10.15 (1H, br.s), 8.39 (1H, s), 8.33-8.31 (1H, m), 7.75-7.85 (1H, m), 7.45-7.3 (2H, m), 7.14 (1H, d), 4.84-4.76 (1H, m), 3.90-3.30 (8H, m) 1.48 (6H, d);

EM (EA) $C_{22}H_{22}N_4O_2$ requiere 374; encontrado 375 $[M+H]^+$.

EJEMPLO 8

Clorhidrato de 6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1H-3-benzazepina



6-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo (preparación 17) (260 mg, 0.537 mmoles) se disolvió en DCM (20 ml) y se trató con ácido trifluoroacético (2 ml, 26.0 mmoles). La mezcla resultante se calentó a reflujo durante 1 hora, después se evaporó. El residuo resultante se dividió entre DCM (10 ml) y NaOH 2N (10 ml). La capa de DCM se recogió, se secó (frita hidrofóbica) y se evaporó. La base libre se disolvió en HCl 4M en dioxano y se evaporó para dar la sal de HCl, clorhidrato de 6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1H-3-benzazepina (225 mg, 0.535 mmoles, 100% de rendimiento) como un polvo blanquecino.

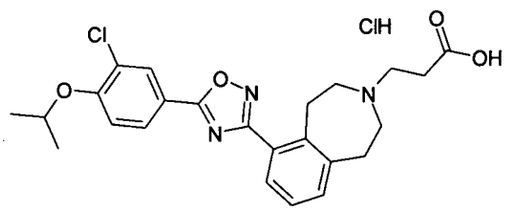
δH (400 MHz, $CDCl_3$) 10.10 (2H, br.s), 8.18 (1H, s), 8.02 (1H, d), 7.82-7.80 (1H, m), 7.33-7.22 (2H, m), 7.05 (1H, d), 5.30 (2H, s), 4.76-4.64 (1H, m), 3.8-3.65 (2H, m), 3.48-3.3 (4H, m), 1.45 (6H, d);

EM (EA) $C_{21}H_{22}{}^{35}ClN_3O_2$ requiere 383; encontrado 384 $[M+H]^+$.

291

EJEMPLO 9

Clorhidrato de ácido 3-[6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]propanoico

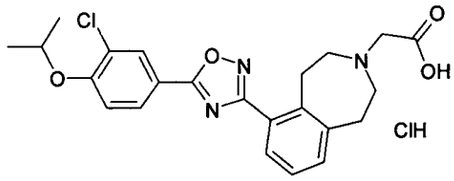


3-[6-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]propanoato de 1,1-dimetiletilo (preparación 18) (25 mg, 0.049 mmoles) se agitó a temperatura ambiente durante 18 horas en HCl 4M en 1,4-dioxano (10 ml). La evaporación y trituración con éter dietílico dio el compuesto del título clorhidrato de de ácido 3-[6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]propanoico (13 mg, 0.026 mmoles, 54.1% de rendimiento) como una goma amarilla.

EM (EA) $C_{24}H_{26}{}^{35}ClN_3O_4$ requiere 455; encontrado 456 $[M+H]^+$.

EJEMPLO 10

Clorhidrato de ácido [6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]acético

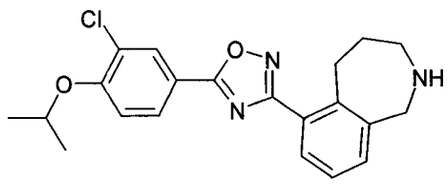


[6-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]acetato de 1,1-dimetiletilo (preparación 19) (120 mg, 0.241 mmoles) se agitó a temperatura ambiente durante 18 horas en HCl 4M en 1,4-dioxano (20 ml). La evaporación y trituración con éter dietílico dio la sal de HCl clorhidrato de de ácido [6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]acético (110 mg, 0.216 mmoles, 90% de rendimiento) como un polvo color crema.

EM (EA) $C_{23}H_{24}{}^{35}ClN_3O_4$ requiere 441; encontrado 442 $[M+H]^+$.

EJEMPLO 11

6-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1*H*-2-benzazepina



A una solución de 3-[2-(aminometil)-6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)fenil]-1-propanol (preparación 23) (105.2 mg, 0.262 mmoles) y trifenilfosfina (343 mg, 1.309 mmoles) en DCM seco (40 ml) a T.A. bajo Ar se añadió DIAD (0.242 ml, 1.243 mmoles) gota a gota y la solución amarillo pálido resultante se agitó a T.A. durante 18 hr. La solución se concentró a ~5 ml, después se hizo pasar un cartucho de SCX-3 (1 g), lavando con MeOH. El producto se eluyó con NH_3 0.5M en MeOH; la concentración bajo vacío dio un aceite amarillo pálido (95.7 mg). La auto-purificación dirigida a la masa por fase inversa dio dos fracciones que contenían el producto deseado, una de ellas se contaminó con $O=PPh_3$. Ambas se añadieron directamente a un cartucho de SCX-2 (10 g), lavando con MeOH. El producto se eluyó con NH_3 0.5M en MeOH; la concentración bajo vacío dio una película amarilla pálida 6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1*H*-2-benzazepina (15.3 mg, 0.034 mmoles, 12.94% de rendimiento).

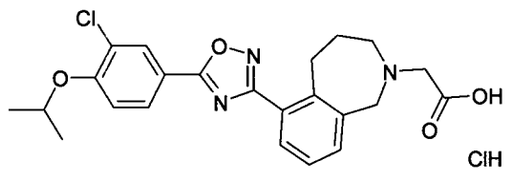
δH (400 MHz, $CDCl_3$) 8.20 (1H, d), 8.04 (1H, dd), 7.69 (1H, d),

7.31 (1H, d), 7.24 (1H, t), 7.05 (1H, d), 4.71 (1H, heptuplete), 4.09 (2H, s), 3.30-3.24 (4H, m), 1.80 (2H, m), 1.44 (6H, d);

EM (EA) $C_{21}H_{22}{}^{35}ClN_3O_2$ requiere 383; encontrado 384 $[M+H]^+$.

EJEMPLO 12

Clorhidrato de ácido [6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]acético



Una mezcla 5:2 de [6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]acetato de 1,1-dimetiletilo y ácido [6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]acético (preparación 24) (21.4 mg) en HCl 4M en dioxano (3 ml) se agitó a T.A. durante 21 horas. La mezcla de reacción se concentró bajo vacío, después se redisolvió en HCl 4M en dioxano (3 ml), y la solución se agitó durante 24 horas adicionales. La concentración bajo vacío dio un aceite amarillo (41 mg), que se trituró con éter (2 x 3 ml) para dejar un sólido blanco clorhidrato de ácido [6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]acético (16.1 mg, 0.031 mmoles, 90% de rendimiento).

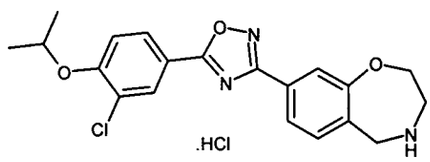
δH (400 MHz, d_6DMSO) 8.17 (1H, d), 8.10 (1H, dd), 7.87 (1H,

dd), 7.58 (1H, d), 7.49 (1H, t), 7.46 (1H, d), 4.89 (1H, heptuplete), 4.69 (2H, s), 4.06 (2H, s), 3.58 (2H, br t), 3.35 (2H, m), 2.00 (2H, br s), 1.36 (6H, d);

EM (EA) $C_{23}H_{24}{}^{35}ClN_3O_4$ requiere 441; encontrado 442 $[M+H]^+$.

EJEMPLO 13

Clorhidrato de 8-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1,4-benzoxazepina



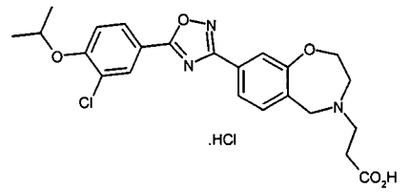
8-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepina-4(5H)-carboxilato de 1,1-dimetiletilo (preparación 34) (0.171 g, 0.352 mmoles) se disolvió en 1,4-dioxano (1 ml) y HCl 4M (4 ml, 16.00 mmoles) en dioxano se añadió. La mezcla de reacción se dejó a temperatura ambiente durante 3 horas. El sólido precipitado resultante se filtró y se lavó con dioxano y éter para dar el compuesto del título (116 mg) como una sal de clorhidrato sólida blanca.

δH (400 MHz, MeOD) 1.42 (6H, d), 3.64 (2H, m), 4.34 (2H, m), 4.48 (2H, s), 4.86 (1H, m), 7.31 (1H, d), 7.59 (1H, d), 7.87 (1H, d), 7.94 (1H, dd), 8.11 (1H, dd), 8.21 (1H, dd);

EM (EA) $C_{20}H_{20}{}^{35}ClN_3O_3$ requiere 385; encontrado 486 $[M+H]^+$.

EJEMPLO 14

Clorhidrato de ácido 3-[8-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]propanoico



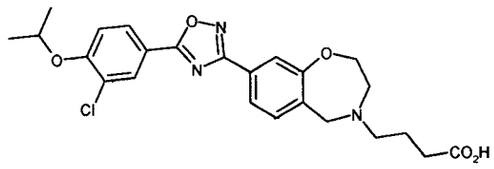
Solución de hidróxido de sodio 2M (ac.) (0.5 ml, 1.000 mmoles) se añadió a una solución de 3-[8-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoato de etilo (preparación 35) (0.09 g, 0.185 mmoles) en etanol (4 ml) y se dejó a temperatura ambiente durante 2 horas. La reacción después se evaporó y el crudo resultante se disolvió en EtOAc/agua (30 ml cada una) y se acidificó con acético ácido. La capa orgánica se secó (sulfato de magnesio) y se evaporó. El crudo resultante se azeotropó con 20 ml de tolueno y el residuo se disolvió en 10 ml de DCM. Se añadió HCl 1M (1 ml) en éter, la mezcla de reacción se evaporó, después se trituró con éter. El compuesto del título (56 mg) se filtró como una sal de clorhidrato de sólida blanquecina.

δH (400 MHz, MeOD) 1.42 (6H, d), 2.92 (2H, t), 3.55 (2H, t), 3.78 (2H, m), 4.40 (2H, m), 4.65 (2H, s), 4.87 (1H, m), 7.31 (1H, d), 7.61 (1H, d), 7.87 (1H, d), 7.96 (1H, dd), 8.11 (1H, dd), 8.21 (1H, d);

EM (EA) $C_{23}H_{24}{}^{35}ClN_3O_5$ requiere 457; encontrado 458 $[M+H]^+$.

EJEMPLO 15

Acido 4-[8-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]butanoico



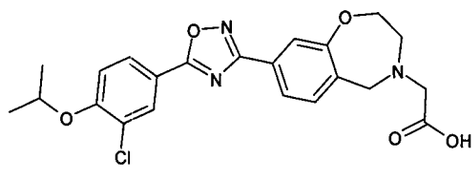
Hidróxido de sodio 2M (ac.) (0.5 ml, 1.000 mmoles) se añadió a una solución de 4-[8-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]butanoato de etilo (preparación 36) (0.103 g, 0.206 mmoles) en etanol (4 ml) y se dejó a temperatura ambiente durante 2 horas. La mezcla de reacción se evaporó y el residuo se disolvió en agua/EtOAc (30 ml cada una) y se acidificó con acético ácido. La capa orgánica se recogió, se secó (sulfato de magnesio), se evaporó y se azeotropó con 15 ml de tolueno. El compuesto del título se obtuvo por trituración con éter y se filtró como un sólido blanco (65 mg).

δH (400 MHz, d_6DMSO) 1.36 (6H, d), 1.70 (2H, m), 2.23 (2H, t), 2.33 (2H, t), 3.02 (2H, m), 3.84 (2H, s), 4.06 (2H, m), 4.89 (1H, m), 7.44 (2H, m), 7.61 (1H, d), 7.72 (1H, dd), 8.10 (1H, dd), 8.18 (1H, d);

EM (EA) $C_{24}H_{26}{}^{35}ClN_3O_5$ requiere 471; encontrado 472 $[M+H]^+$.

EJEMPLO 16

Acido [8-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]acético



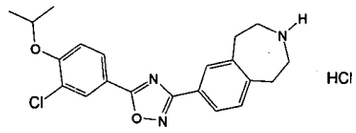
[8-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]acetato de 1,1-dimetiletilo (preparación 37) (0.13 g, 0.260 mmoles) se disolvió en 1,4-dioxano (1 ml) y HCl 4M (4 ml, 16.00 mmoles) en dioxano se añadió y la mezcla de reacción se dejó a temperatura ambiente durante 24 horas. Después, la mezcla de reacción se evaporó, se trituró con éter y el sólido resultante se filtró. El sólido se disolvió en 5 ml de hidróxido de sodio 2M y se acidificó con acético ácido cuando el sólido se separó. Se trató de disolver en EtOAc but era insoluble, por lo que se filtró y se lavó bien con agua, acetona y éter para dar el compuesto del título (44 mg) como un sólido blanco.

δH (400 MHz, d_6DMSO) 1.36 (6H, d), 3.13 (2H, br. s), 3.96 (2H, s), 4.08 (2H, br. s), 4.89 (1H, m), 7.38 (1H, d), 7.44 (1H, d), 7.61 (1H, s), 7.72 (1H, d), 8.11 (1H, d), 8.18 (1H, d), (señal 2H restante oscurecida por pico de solvente);

EM (EA) $C_{22}H_{22}{}^{35}ClN_3O_5$ requiere 443; encontrado 444 $[M+H]^+$.

EJEMPLO 17

Clorhidrato de 7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1H-3-benzazepina



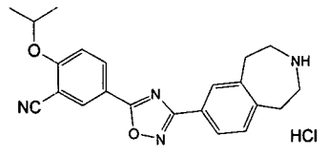
Una solución de 7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo (preparación 42) (950 mg, 1.963 mmoles) en ácido clorhídrico (una solución 4M en dioxano, 10 ml, 40.0 mmoles) y 1,4-dioxano (10 ml) se agitó a temperatura ambiente durante 5 horas (un precipitado se había formado). La mezcla de reacción se filtró y se lavó con dioxano (~5 ml), y el sólido se secó bajo vacío (con pistola) durante la noche para dar el compuesto del título (711 mg, 1.607 mmoles, 82% de rendimiento) como un sólido blanco.

δH ($CDCl_3$, 400 MHz): 10.17 (2H, br s), 8.25 (1H, d), 8.06 (1H, dd), 7.98-8.03 (2H, m), 7.33 (1H, d), 7.06 (1H, d), 4.72 (1H, heptuplete), 3.35-3.47 (8H, m), 1.46 (6H, d).

EM (EA): $C_{21}H_{22}{}^{35}ClN_3O_2$ requiere 383; encontrado 384 $[M+H]^+$.

EJEMPLO 18

Clorhidrato de 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)-1,2,4-oxadiazol-5-il]benzonitrilo



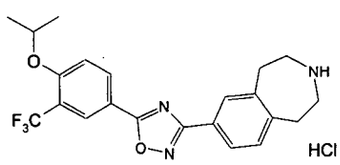
7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo (preparación 43) (735 mg, 1.55 mmoles) se disolvió en HCl 4M en dioxano y la solución se agitó durante 1 hr. El compuesto del título se filtró como un sólido blanco y se secó en un horno de vacío (462 mg, 1.13 mmoles).

δH (d_6DMSO, 400 MHz): 9.24 (2H, brs), 8.51 (1H, d), 8.40 (1H, dd), 7.95 (1H, d), 7.92 (1H, dd), 7.57 (1H, d), 7.45 (1H, d), 4.98 (1H, heptuplete), 3.28-3.18 (8H, m), 1.39 (6H, d).

EM (EA): $C_{22}H_{22}N_4O_2$ requiere 374; encontrado 375 $[M+H]^+$.

EJEMPLO 19

Clorhidrato de 7-{5-[4-[(1-metiletil)oxi]-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-2,3,4,5-tetrahidro-1H-3-benzazepina



7-{5-[4-[(1-Metiletil)oxi]-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-

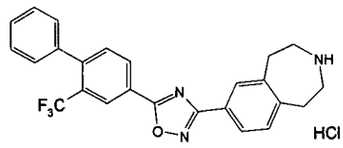
il}-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo (preparación 44) (550 mg, 1.06 mmoles) se disolvió en HCl 4M en dioxano (5 ml) y la solución se agitó durante 2 hr. El compuesto del título se filtró como un sólido blanco y se secó en un horno de vacío (259 mg, 0.57 mmoles).

δH (d_6DMSO, 400 MHz): 9.23 (2H, brs), 8.40 (1H, dd), 8.31 (1H, d), 7.96 (1H, d), 7.93 (1H, dd), 7.59 (1H, d), 7.44 (1H, d), 4.98 (1H, heptuplete), 3.27-3.18 (8H, m), 1.36 (6H, d);

EM (EA): $C_{22}H_{22}F_3N_3O_2$ requiere 417; encontrado 418 $[M+H]^+$.

EJEMPLO 20

Clorhidrato de 7-{5-[2-(trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-2,3,4,5-tetrahidro-1H-3-benzazepina



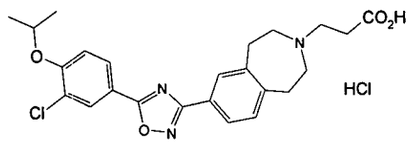
7-{5-[2-(Trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo (preparación 45) (440 mg, 0.82 mmoles) se disolvió en HCl 4M en dioxano (3 ml) y la solución se agitó durante 2 hr. El compuesto del título se filtró como un sólido blanco (376 mg, 0.82 mmoles).

δH (d_6DMSO, 400 MHz): 9.27 (2H, brs), 8.53 (1H, d), 8.51 (1H, dd), 8.01 (1H, d), 7.97 (1H, dd), 7.74 (1H, d), 7.54-7.50 (3H, m), 7.47 (1H, d), 7.43-7.39 (2H, m), 3.28-3.20 (8H, m).

EM (EA): $C_{25}H_{20}F_3N_3O$ requiere 435; encontrado 436 $[M+H]^+$.

EJEMPLO 21

Acido 3-[7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]propanoico



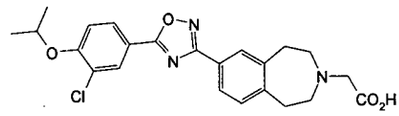
Una mezcla de clorhidrato de 7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1H-3-benzazepina (ejemplo 17) (200 mg, 0.52 mmoles), 2-propenoato de 1,1-dimetiletilo (151 µl, 1.04 mmoles) y diisopropiletilamina (453 µl, 2.60 mmoles) en metanol (5 ml) se calentó en el microondas a 90°C durante 30 minutos antes de que el solvente se removiera bajo vacío. El residuo se disolvió en HCl 4M (2 ml) en dioxano y la mezcla se agitó a temperatura ambiente durante 5 hr. El solvente se removió bajo vacío y el residuo se purificó por PADM. Al producto que contenía fracciones se añadió HCl 2M y la solución se concentró bajo vacío para dar el compuesto del título como un sólido blanco (116 mg, 0.24 mmoles).

δH (d_6DMSO, 400 MHz): 12.73 (1H, br.s), 10.76 (1H, br.s), 8.19 (1H, d), 8.11 (1H, dd), 7.98 (1H, d), 7.93 (1H, dd), 7.46 (1H, d), 7.45 (1H, d), 4.89 (1H, heptuplete), 3.76-3.64 (2H, m), 3.44-3.31 (4H, oculto bajo el pico de H_2O), 3.25-3.03 (4H, m), 2.89 (2H, t), 1.37 (6H, d).

EM (EA): $C_{24}H_{26}{}^{35}ClN_3O_4$ requiere 455; encontrado 456 $[M+H]^+$.

EJEMPLO 22

Acido [7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]acético



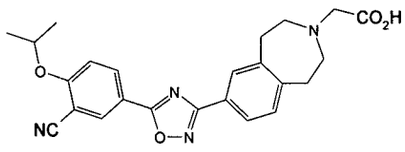
Una solución de [7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]acetato de etilo (preparación 46) (77 mg, 0.164 mmoles) en metanol (30 ml) se agitó a temperatura ambiente y se añadió hidróxido de sodio (3 ml, 6.00 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante la noche. El solvente se removió bajo vacío, el sólido se trituró con metanol (~5 ml) y el sólido resultante se filtró y se secó. El sólido se suspendió en metanol (~30 ml) y se añadió acético ácido para llevar el pH de la solución a 5-6, el solvente se removió bajo vacío. El residuo resultante se disolvió en DCM (~30 ml) y agua (~30 ml) y las capas se dividieron. La capa acuosa se volvió a extraer con DCM (~20 ml) y los compuestos orgánicos combinados se hicieron pasar a través de un cartucho de separación de fase y el solvente se redujo bajo vacío. El residuo resultante se secó en una pistola de secado a 60°C para dar el compuesto del título (22 mg, 0.047 mmoles, 29% de rendimiento) como un sólido blanquecino.

δH (d_6DMSO, 400 MHz): 8.19 (1H, s), 8.11 (1H, d), 7.82-7.90 (2H, m), 7.44 (1H, d), 7.36 (1H, d), 4.89 (1H, heptuplete), 3.34 (2H, s), 3.07-2.98 (4H, m), 2.91-2.86 (4H, m), 1.37 (6H, d).

EM (EA^+): $C_{23}H_{24}{}^{35}ClN_3O_4$ requiere 441; encontrado 442 $[M+H]^+$.

EJEMPLO 23

Acido [7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3*H*-3-benzazepin-3-il]acético



Una mezcla de [7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3*H*-3-benzazepin-3-il]acetato de etilo (preparación 47) (43 mg, 0.09 mmoles), hidróxido de sodio acuoso (2M, 430 µl, 0.86 mmoles) y etanol (4.3 ml) se calentó a 40°C durante 1 hr. La mezcla de reacción se enfrió a temperatura ambiente y se concentró. El residuo se recogió en agua, que después se acidificó a pH 6 con ácido acético. La fase acuosa se extrajo con EtOAc (2 x 20 ml) y las fracciones orgánicas combinadas se concentraron para dar un sólido blanco, que después se trituró con EtOAc para dar el compuesto del título como un sólido blanco (36 mg, 0.08 mmoles).

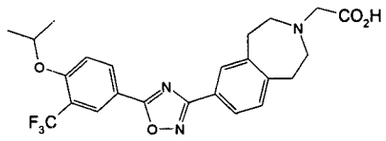
δH (d_6DMSO, 400 MHz): 8.50 (1H, d), 8.41 (1H, dd), 7.85-7.80 (2H, m), 7.55 (1H, d), 7.32 (1H, d), 4.98 (1H, heptuplete), 3.00-2.91 (6H, m),

2.75-2.66 (4H, m), 1.39 (6H, d);

EM (EA-): $C_{24}H_{24}N_4O_4$ requiere 432; encontrado 431 [M-H$^+$].

EJEMPLO 24

Acido (7-{5-[4-[(1-metiletil)oxi]-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3*H*-3-benzazepin-3-il)acético



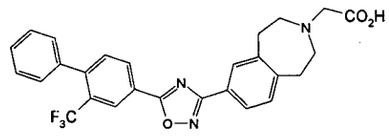
Una mezcla de (7-{5-[4-[(1-metiletil)oxi]-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3*H*-3-benzazepin-3-il)acetato de etilo (preparación 48) (59 mg, 0.12 mmoles), hidróxido de sodio acuoso (2M, 590 µl, 1.18 mmoles) y etanol (6 ml) se calentó a 40°C durante 1 hr. La mezcla de reacción se enfrió a temperatura ambiente y se concentró. El residuo se recogió en agua, que después se acidificó a pH 6 con ácido acético. La fase acuosa se extrajo con EtOAc (2 x 20 ml) antes de que las fracciones orgánicas combinadas se concentraran y el residuo se trituró con EtOAc y el compuesto del título se filtró y se secó en un horno de vacío para dar un sólido blanco (36 mg, 0.08 mmoles).

δH (d_6DMSO, 400 MHz): 8.41 (1H, dd), 8.30 (1H, d), 7.88-7.82 (2H, m), 7.58 (1H, d), 7.35 (1H, d), 4.98 (1H, heptuplete), 3.25 (2H, s), 3.06-2.96 (4H, m), 2.89-2.81 (4H, m), 1.36 (6H, d);

EM (EA-): $C_{24}H_{24}F_3N_3O_4$ requiere 475; encontrado 474 [M-H$^+$].

EJEMPLO 25

Acido (7-{5-[2-(trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3*H*-3-benzazepin-3-il) acético



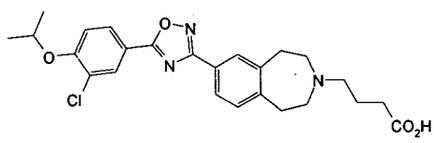
Una mezcla de (7-{5-[2-(trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3*H*-3-benzazepin-3-il)acetato de etilo (preparación 49) (22 mg, 0.04 mmoles), hidróxido de sodio acuoso (2M, 220 µl, 0.44 mmoles) y etanol (2.2 ml) se calentó a 40°C durante 1 hr. La mezcla de reacción se enfrió a temperatura ambiente y se concentró. El residuo se recogió en agua, que después se acidificó a pH 6 con ácido acético. La fase acuosa se extrajo con EtOAc (2 x 20 ml) antes de que las fracciones orgánicas combinadas se concentraran y el residuo se trituró con EtOAc y el compuesto del título se filtró y se secó en un horno de vacío para dar un sólido blanco (13 mg, 0.03 mmoles).

δH (d_6DMSO, 400 MHz): 8.52 (1H, d), 8.50 (1H, dd), 7.92-7.86 (2H, m), 7.73 (1H, d), 7.54-7.49 (3H, m), 7.44-7.35 (3H, m), 3.18 (2H, s), 3.05-2.96 (4H, m), 2.85-2.79 (4H, m);

EM (EA-) : $C_{27}H_{22}F_3N_3O_3$ requiere 493; encontrado 492 [M-H^+].

EJEMPLO 26

Acido 4-[7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]butanoico



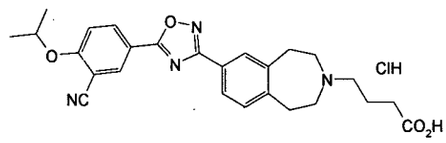
Una solución de 4-[7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]butanoato de etilo (preparación 50) (100 mg, 0.201 mmoles) en etanol (6 ml) se agitó a temperatura ambiente y se añadió hidróxido de sodio (1.5 ml, 3.00 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 90 min y después se acidificó con ácido acético a pH 5, y la mezcla se concentró bajo vacío. El residuo resultante se disolvió en EtOAc (~30 ml) y agua (~30 ml) y las capas se dividieron, la capa acuosa se volvió a extraer con EtOAc (~20 ml) y los compuestos orgánicos combinados se hicieron pasar a través de un cartucho de separación de fase y el solvente se redujo bajo vacío. El residuo se purificó por trituración con metanol, el sólido se filtró y se secó durante el concrecionamiento para dar el compuesto del título (30 mg, 0.061 mmoles, 30% de rendimiento).

δH (d_6DMSO, 400 MHz): 8.19 (1H, s), 8.11 (1H, d), 7.79-7.90 (2H, m), 7.44 (1H, d), 7.34 (1H, d), 4.89 (1H, heptuplete), 3.46-3.24 (2H, oculto bajo el pico de H_2O), 3.01-2.93 (4H, m), 2.68-2.59 (4H, m), 2.28 (2H, t), 1.70 (2H, quintuplete) 1.37 (6H, d).

EM (EA): $C_{25}H_{28}{}^{35}ClN_3O_4$ requiere 469; encontrado 470 $[M+H]^+$.

EJEMPLO 27

Clorhidrato de ácido 4-[7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]butanoico



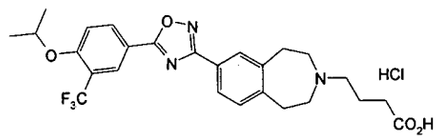
Una solución de 4-[7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]butanoato de etilo (preparación 51) (218 mg, 0.446 mmoles) en etanol (6 ml) se agitó a temperatura ambiente y se añadió hidróxido de sodio (2 ml, 4.00 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 90 minutos y después se acidificó con ácido acético a pH 5, y la mezcla se concentró bajo vacío. El residuo resultante se disolvió en EtOAc (~30 ml) y agua (~30 ml) y las capas se dividieron, la capa acuosa se volvió a extraer con EtOAc (~20 ml) y los compuestos orgánicos combinados se hicieron pasar a través de un cartucho de separación de fase y el solvente se redujo bajo vacío. El residuo se purificó mediante la adición de 10 gotas de HCl 2M en éter, seguido por trituración con éter, el sólido se filtró y se secó durante el concrecionamiento y después bajo vacío a 60°C para dar el compuesto del título (68 mg, 0.130 mmoles, 29% de rendimiento).

δH (d_6DMSO, 400 MHz): 8.51 (1H, s), 8.40 (1H, d), 7.97 (1H, s),

7.93 (1H, d), 7.56 (1H, d), 7.47 (1H, d), 4.99 (1H, heptuplete), 3.07-3.80 (10H, m), 2.35 (2H, t), 1.92-2.02 (2H, m), 1.39 (6H, d); EM (EA): $C_{26}H_{28}N_4O_4$ requiere 460; encontrado 461 $[M+H]^+$.

EJEMPLO 28

Clorhidrato de de ácido 4-(7-{5-[4-[(1-metiletil)oxi]-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il)butanoico



Una solución de 4-(7-{5-[4-[(1-metiletil)oxi]-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il)butanoato de etilo (preparación 52) (181 mg, 0.341 mmoles) en etanol (6 ml) se agitó a temperatura ambiente y se añadió hidróxido de sodio (2 ml, 4.00 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 90 minutos. La mezcla de reacción se acidificó con ácido acético a pH 5, y la mezcla se concentró bajo vacío. El residuo resultante se disolvió en acetato de etilo (~30 ml) y agua (~30 ml) y las capas se dividieron, la fase acuosa se volvió a extraer con acetato de etilo (~20 ml) y los compuestos orgánicos combinados se hicieron pasar a través de un cartucho de separación de fase y el solvente se redujo bajo vacío.

El residuo se purificó mediante la adición de 10 gotas de HCl 2M en éter, seguido por trituración con éter, el sólido se filtró y se secó durante el

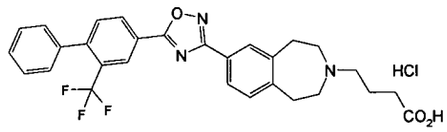
concrecionamiento para dar el compuesto del título (119 mg, 0.21 mmoles, 62% de rendimiento).

δH (d_6DMSO, 400 MHz): 8.40 (1H, d), 8.32 (1H, s), 7.97 (1H, s), 7.94 (1H, d), 7.59 (1H, d), 7.45 (1H, d), 4.98 (1H, heptuplete), 3.09-3.82 (10H, m), 2.35 (2H, t), 1.90-2.01 (2H, m), 1.36 (6H, d);

EM (EA) : $C_{26}H_{28}F_3N_3O_4$ requiere 503; encontrado 504 $[M+H]^+$.

EJEMPLO 29

Clorhidrato de ácido 4-(7-{5-[2-(trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il)butanoico



Una solución de 4-(7-{5-[4-{(1E)-1-[(1Z)-1-propen-1-il]-1,3-butadien-1-il}-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il)butanoato de etilo (preparación 53) (277 mg, 0.504 mmoles) en etanol (6 ml) se agitó a temperatura ambiente y se añadió hidróxido de sodio (2 ml, 4.00 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 90 minutos y después se acidificó con ácido acético a pH 5, y la mezcla se concentró bajo vacío. El residuo resultante se disolvió en EtOAc (~30 ml) y agua (~30 ml) y las capas se dividieron, la capa acuosa se volvió a extraer con EtOAc (~20 ml) y los compuestos orgánicos combinados se hicieron pasar a través de un cartucho de separación de fase y el solvente

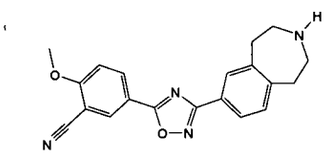
se redujo bajo vacío. El residuo se purificó mediante la adición de 10 gotas de HCl 2M en éter, seguido por trituración con éter, el sólido se filtró y se secó durante el concrecionamiento y durante la noche bajo vacío a 60ºC para dar el compuesto del título (120 mg, 0.20 mmoles, 41% de rendimiento).

δH (d_6DMSO, 400 MHz): 8.53 (1H, s), 8.50 (1H, d), 8.01 (1H, s), 7.97 (1H, d), 7.75 (1H, d), 7.37-7.56 (6H, m), 3.14-3.41 (8H, m), 3.07 (2H, br s), 2.34 (2H, t), 1.87-1.99 (2H, m).

EM (EA) : $C_{29}H_{26}F_4N_3O_3$ requiere 521; encontrado 522 $[M+H]^+$.

EJEMPLO 30

Clorhidrato de 2-(metiloxi)-5-[3-(2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)-1,2,4-oxadiazol-5-il]benzonitrilo



Una solución de 7-{5-[3-ciano-4-(metiloxi)fenil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo (preparación 54) (280 mg, 0.627 mmoles) en solución de ácido clorhídrico 4M en dioxano (5 ml, 20.00 mmoles) y 1,4-dioxano (5 ml) se agitó a temperatura ambiente durante la noche. La mezcla de reacción se filtró y se lavó con dioxano (~5 ml), y el sólido se seco bajo vacío para dar el compuesto del título (177 mg, 0.393 mmoles, 62.7% de rendimiento) como un sólido blanquecino.

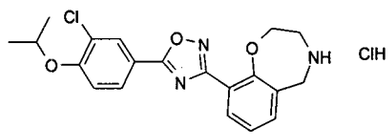
δH (d_6DMSO, 400 MHz): 8.99-9.31 (2H, m), 8.53 (1H, s), 8.46

(1H, d), 7.96 (1H, s), 7.93 (1H, d), 7.54 (1H, d), 7.46 (1H, d), 4.07 (3H, s), 3.09-3.31 (7H, m);

EM (EA): $C_{20}H_{18}N_4O_2$ requiere 346; encontrado 347 $[M+H]^+$.

EJEMPLO 31

Clorhidrato de 9-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1,4-benzoxazepina



9-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepina-4(5H)-carboxilato de 1,1-dimetiletilo (preparación 66) (320 mg, 0.658 mmoles) se disolvió en 1,4-dioxano (1 ml) y se trató con HCl (2 ml, 8.00 mmoles) en 1,4-dioxano. La mezcla de reacción se dejó a T.A. durante 1 hr, se evaporó y después se trituró con éter para dar el compuesto del título (180 mg) como un sólido blanco.

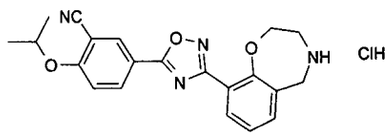
EM (EA): $C_{20}H_{20}{}^{35}ClN_3O_3$ requiere 385; encontrado 386 $[M+H]^+$.

El siguiente compuesto se preparó por un método similar.

313

EJEMPLO 32

Clorhidrato de 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1,4-benzoxazepin-9-il)-1,2,4-oxadiazol-5-il]benzonitrilo

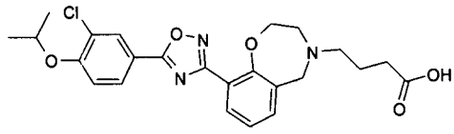


Se preparó de una manera similar al ejemplo 31 a partir de la preparación 67.

EM (EA): $C_{21}H_{20}N_4O_3$ requiere 376; encontrado 377 $[M+H]^+$.

EJEMPLO 33

Acido 4-[9-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]butanoico



Una solución de 4-[9-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]butanoato de etilo (preparación 68) (130 mg, 0.260 mmoles) en etanol se trató con hidróxido de sodio (10.4 mg en 1 ml, 0.260 mmoles). La mezcla de reacción se dejó reposar a T.A. durante 1 hora después se evaporó. El crudo resultante se dividió entre EtOAc/agua, se acidificó con ácido acético, se separó y los compuestos orgánicos se secaron sobre sulfato de magnesio y se evaporaron.

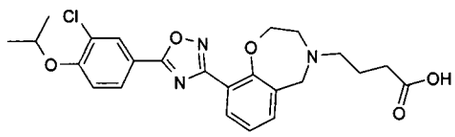
El compuesto del título (61 mg) se obtuvo por trituración con éter como un sólido blanco.

δH (d_6DMSO, 400 MHz): 1.36 (6H, d), 1.69 (2H, m), 2.23 (2H, t), 2.43 (2H, t), 3.05 (2H, m), 3.86 (2H, s), 4.07 (2H, m), 4.88 (1H, m), 7.20 (1H, t), 7.43-7.49 (2H, m), 7.78 (1H, dd), 8.09 (1H, dd), 8.17 (1H, d), 12.10 (1H, br. s);

EM (EA-): $C_{24}H_{26}{}^{35}ClN_3O_5$ requiere 471; encontrado 470 [M-H^+].

EJEMPLO 33 Preparación alternativa

Acido 4-[9-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]butanoico



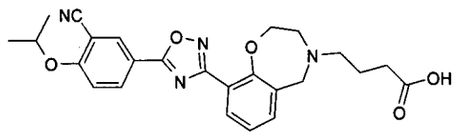
Una solución de 4-[9-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]butanoato de etilo (preparación 68) (61.7 g, 123 mmoles) en etanol (600 ml) se trató con hidróxido de sodio 2M (123 ml, 247 mmoles) y la mezcla se agitó a temperatura ambiente durante la noche. El solvente se evaporó y el residuo se disolvió en agua (1 litro). La solución acuosa se enfrió en hielo/agua y se trató lentamente con ácido acético glacial (28.3 ml, 494 mmoles). La goma resultante se agitó vigorosamente hasta que sólido filtrable se obtuvo, que después se recogió por filtración y se lavó con más agua (2x 500 ml).

Después de aspirar la almohadilla de secado, el material se disolvió en una mezcla de 95:5 de diclorometano/metanol y se secó (sulfato de sodio). El solvente se removió por evaporación y el sólido resultante se trituró bajo éter dietílico (200 ml), se recogió por filtración, se lavó con éter dietílico y se secó para dar el compuesto del título como un sólido incoloro (54 g).

EM (EA) $C_{24}H_{26}{}^{35}ClN_3O_5$ requiere 471; encontrado 472 $[M+H]^+$.

EJEMPLO 34

Acido 4-[9-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]butanoico



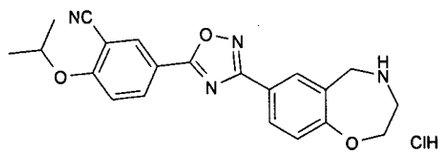
Se preparó de una manera similar al ejemplo 33 a partir de la preparación 69.

δH (d_6DMSO, 400 MHz): 1.38 (6H, d), 1.69 (2H, m), 2.23 (2H, t), 2.43 (2H, t), 3.05 (2H, m), 3.86 (2H, s), 4.07 (2H, m), 4.98 (1H, m), 7.20 (1H, t), 7.47 (1H, dd), 7.54 (1H, d), 7.77 (1H, dd), 8.38 (1H, dd), 8.49 (1H, d), 12.10 (1H, br. s);

EM (EA): $C_{25}H_{26}N_4O_5$ requiere 462; encontrado 463 $[M+H]^+$.

EJEMPLO 35

Clorhidrato de 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1,4-benzoxazepin-7-il)-1,2,4-oxadiazol-5-il]benzonitrilo



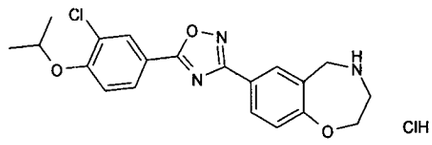
7-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepina-4(5H)-carboxilato de 1,1-dimetiletilo (preparación 76) (0.410 g, 0.860 mmoles) se disolvió en 1,4-dioxano (1 ml). Se añadió HCl (1 ml, 4.00 mmoles) en dioxano (4M) y se agitó a T.A. durante 2 horas. Se añadió éter, se filtró y se secó en el horno bajo vacío a T.A. para dar 0.26 g de sólido blanco. 50 mg se purificaron por PADM para dar el compuesto del título (13 mg) como un sólido color crema.

δH (MeOD, 400 MHz): 1.44 (6H, d), 3.63 (2H, m), 4.33 (2H, m), 4.52 (2H, s), 4.92 (1H, m), 7.30 (1H, d), 7.43 (1H, d), 8.15 (1H, dd), 8.21 (1H, d), 8.38 (1H, dd), 8.45 (1H, d) ;

EM (EA): $C_{21}H_{20}N_4O_3$ requiere 376; encontrado 377 $[M+H]^+$.

EJEMPLO 36

Clorhidrato de 7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1,4-benzoxazepina



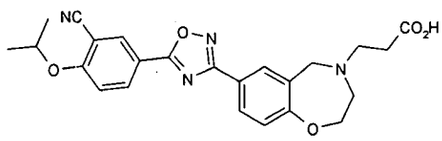
Se preparó por un método similar ald el ejemplo 35 a partir de la preparación 77.

δH (d_6DMSO, 400 MHz): 1.35 (6H, d), 3.51 (3H, m), 4.31 (2H, m), 4.82 (2H, s), 4.85 (1H, m), 7.23 (1H, d), 7.45 (1H, d), 7.97-8.12 (2H, m), 8.18 (2H, m) ;

EM (EA): $C_{20}H_{20}{}^{35}ClN_3O_3$ requiere 385; encontrado 386 $[M+H]^+$.

EJEMPLO 37

Acido 3-[7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]propanoico



3-[7-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoato de etilo (preparación 78) (0.092 g, 0.193 mmoles) se disolvió en etanol (2 ml). Después, NaOH 2N (1 ml, 2.000 mmoles) se añadió y la mezcla de reacción se dejó reposar a T.A. durante 2

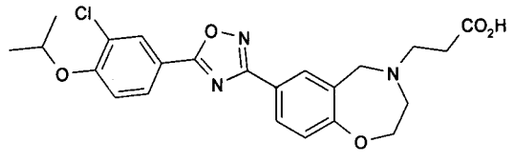
horas. Etanol se removió por evaporación y el residuo resultante se disolvió en EtOAc y agua, se acidificó con ácido acético y las capas se separaron. El sólido se separó de la fase acuosa y el sólido se filtró y se secó bajo vacío durante la noche a 50°C para dar el compuesto del título (8 mg) como un sólido blanco.

δH (d_6DMSO, 400 MHz): 1.37 (6H, d), 2.38 (2H, t), 2.67 (2H, m), 3.03 (2H, m), 3.89 (2H, s), 4.07 (2H, m), 4.97 (1H, m), 7.14 (1H, d), 7.54 (1H, d), 7.89 (1H, dd), 7.98 (1H, d), 8.39 (1H, dd), 8.51 (1H, d);

EM (EA): $C_{24}H_{24}N_4O_5$ requiere 448; encontrado 449 $[M+H]^+$.

EJEMPLO 38

Acido 3-[7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]propanoico



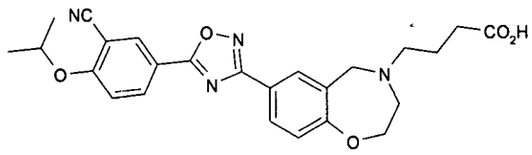
Se preparó por un método similar al del ejemplo 37 a partir de la preparación 79.

δH (d_6DMSO, 400 MHz): 1.36 (6H, d), 2.43 (2H, t), 2.70 (2H, m), 3.04 (2H, m), 3.91 (2H, s), 4.07 (2H, m), 4.87 (1H, m), 7.14 (1H, d), 7.43 (1H, d), 7.89 (1H, dd), 7.99 (1H, d), 8.09(1H, dd), 8.18 (1H, d);

EM (EA): $C_{23}H_{24}{}^{35}ClN_3O_5$ requiere 457; encontrado 458 $[M+H]^+$.

EJEMPLO 39

Acido 4-[7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]butanoico



4-[7-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]butanoato de etilo (preparación 80) (0.084 g, 0.171 mmoles) se disolvió en etanol (2 ml). Después, NaOH 2N (1 ml, 2.000 mmoles) se añadió y la reacción se dejó reposar a T.A. durante 3 horas. El etanol se removió por evaporación y el residuo resultante se disolvió en EtOAc y agua, se acidificó con ácido acético y las fases se separaron. La fase orgánica se secó ($MgSO_4$), se evaporó y se trituró con éter. El secado bajo vacío durante la noche a 50°C dio el compuesto del título (22 mg) como un sólido blanco.

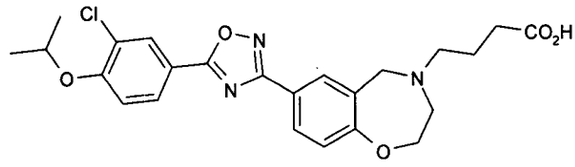
δH (d_6DMSO, 400 MHz): 1.37 (6H, d), 1.66 (2H, t), 2.22 (2H, t), 2.45 (2H, m), 3.01 (2H, m), 3.82 (2H, s), 4.07 (2H, m), 4.95 (1H, m), 7.14 (1H, d), 7.54 (1H, d), 7.89 (1H, dd), 7.96 (1H, d), 8.38(1H, dd), 8.50 (1H, d);

EM (EA): $C_{25}H_{26}N_4O_5$ requiere 462; encontrado 463 $[M+H]^+$.

320

EJEMPLO 40

Acido 4-[7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]butanoico



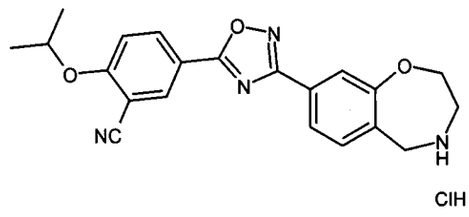
Se preparó por hidrólisis del éster, preparación 81, usando el método descrito para el ejemplo 37.

δH (d_6DMSO, 400 MHz): 1.36 (6H, d), 1.68 (2H, t), 2.23 (2H, t), 2.45 (2H, m), 3.01 (2H, m), 3.87 (2H, s), 4.07 (2H, m), 4.87 (1H, m), 7.13 (1H, d), 7.43 (1H, d), 7.89 (1H, dd), 7.95 (1H, d), 8.09 (1H, dd), 8.52 (1H, d);

EM (EA): $C_{24}H_{26}{}^{35}ClN_3O_5$ requiere 471; encontrado 472 $[M+H]^+$.

EJEMPLO 41

2-[(1-Metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1,4-benzoxazepin-8-il)-1,2,4-oxadiazol-5-il]benzonitrilo

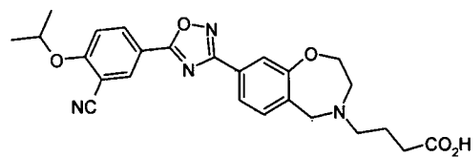


Se preparó a partir de la preparación 82 usando un procedimiento similar al del ejemplo 35.

EM (EA): $C_{21}H_{20}N_4O_3$ requiere 376; encontrado 377 $[M+H]^+$.

EJEMPLO 42

Acido 4-[8-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]butanoico



Se preparó a partir de la preparación 83 usando el método descrito en el ejemplo 15.

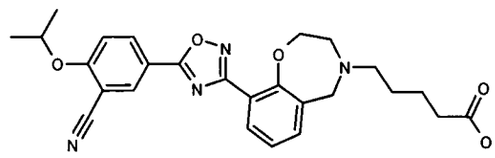
δH (d_6DMSO, 400 MHz): 1.38 (6H, d), 1.69 (2H, m), 2.21 (2H, t), 2.42 (2H, t), 3.02 (2H, m), 3.84 (2H, s), 4.06 (2H, m), 4.97 (1H, m), 7.44 (1H, d), 7.54 (1H, d), 7.61 (1H, d), 7.71 (1H, dd), 8.39 (1H, dd), 8.50 (1H, d), 12.10 (1H, br.s);

EM (EA): $C_{25}H_{26}N_4O_5$ requiere 462; encontrado 463 $[M+H]^+$.

322

EJEMPLO 43

Acido 5-[9-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]pentanoico



Hidróxido de sodio 2M (0.347 ml, 0.694 mmoles) se añadió a una solución agitada de 5-[9-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]pentanoato de etilo (preparación 93) (70 mg, 0.139 mmoles) en etanol (5 ml) y la mezcla se calentó a 60°C durante la noche. La mezcla de reacción se dejó enfriar a temperatura ambiente y el solvente se evaporó. El residuo se diluyó con agua, se acidificó con ácido clorhídrico 2M y se extrajo con acetato de etilo. La fase orgánica se lavó con agua, se secó y se evaporó para dar el producto como un sólido blanquecino (20 mg).

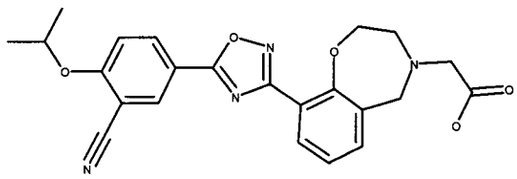
δH (400 MHz, $CDCl_3$). 1.47 (6h, d), 1.59-1.70 (4H, m), 2.3 (2H, t), 2.61 (2H, t), 3.25-3.29 (2H, m), 4.05 (2H, s), 4.24-4.28 (2H, m), 4.79 (1H, m), 7.12 (1H, d), 7.20 (1H, dd), 7.39 (1H, d), 7.95 (1H, d), 8.30 (1H, dd), 8.43 (1H, s).

EM (EA) $C_{26}H_{28}N_4O_5$ requiere 476 Encontrado 477 $[M+H]^+$.

323

EJEMPLO 44

Acido [9-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]acético



Hidróxido de sodio 2M (0.54 ml, 1.08 mmoles) se añadió a una solución agitada de [9-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]acetato de etilo (preparación 86) (100 mg, 0.216 mmoles) en etanol (10 ml) y la mezcla se agitó a temperatura ambiente durante 2 hr. El solvente se evaporó antes de diluirse con agua, se acidificó con ácido clorhídrico 2M y se extrajo con acetato de etilo. El extracto orgánico se lavó con agua, se secó y se evaporó para dar el producto como un sólido blanquecino (30 mg).

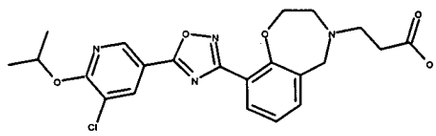
δH (400 MHz, D_6-DMSO). 1.39 (6H, d), 3.88-4.02 (2H,m), 4.09-4.13 (2H, m), 4.98 (1H, m), 7.43 (1H, d), 7.56 (1H, d), 7.82 (1H, d), 8.39 (1H, d), 8.50 (1H, s). Los picos faltantes fueron oscurecidos por agua y solvente residual.

EM (EA) $C_{23}H_{22}N_4O_5$ requiere 434; encontrado 435 $[M+H]^+$.

324

EJEMPLO 45

Acido 3-[9-(5-{5-cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoico



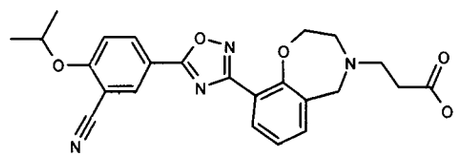
3-[9-(5-{5-Cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoato de etilo (preparación 91) (28 mg, 0.058 mmoles) se disolvió en etanol (5 ml). Hidróxido de sodio 2M (0.144 ml, 0.288 mmoles) se añadió y la mezcla de reacción se agitó a 60°C durante 4 horas. El solvente se evaporó y la mezcla de reacción se diluyó con agua, se neutralizó con ácido clorhídrico 2M y se extrajo con acetato de etilo. La fase orgánica se lavó con agua, se secó y se evaporó para dar el producto como un sólido blanco (26 mg).

δH (400 MHz, $CDCl_3$). 1.46 (6H, d), 2.54 (2H, br t), 2.91 (2H, br t), 3.36 (2H, m), 4.12 (2H, s), 4.28 (2H , br m), 5.48 (1H, m), 7.21-7.29 (1H, m), 7.39 (1H, d), 8.00 (1H, d), 8.38 (1H, s), 8.88 (1H, s).

EM (EA) $C_{22}H_{23}{}^{35}ClN_4O_5$ requiere 458 Encontrado 459 $[M+H]^+$.

EJEMPLO 46

Acido 3-[9-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoico



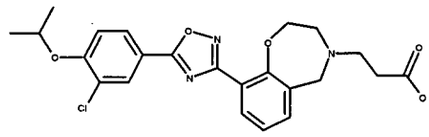
3-[9-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoato de etilo (preparación 92) (40 mg, 0.084 mmoles) se disolvió en etanol (5 ml). Hidróxido de sodio 2M (0.210 ml, 0.420 mmoles) se añadió y la mezcla de reacción se agitó a 60°C durante 4 horas. El solvente se evaporó, después la mezcla de reacción se diluyó con agua, se neutralizó con ácido clorhídrico 2M y se extrajo con acetato de etilo. La fase orgánica se lavó con agua, se secó y se evaporó para dar el producto como un sólido incoloro (16 mg).

δH (400 MHz, $CDCl_3$). 1.47 (6H, d), 2.56 (2H, br t), 2.92 (2H, br t), 3.34-3.39 (2H, m), 4.13 (2H, br s), 4.25-4.31 (2H, m), 4.79 (1H, m), 7.13 (1H, d), 7.20-7.28 (1H, m), 7.40 (1H, d), 8.00 (1H, d), 8.33 (1H, d), 8.42 (1H, s).

EM (EA) $C_{22}H_{24}N_4O_5$ requiere 448; encontrado 449 $[M+H]^+$.

EJEMPLO 47

Acido 3-[9-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoico



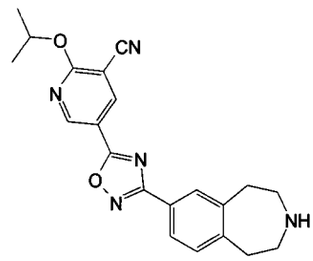
3-[9-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoato de etilo (preparación 88) (60 mg, 0.123 mmoles) se disolvió en etanol (5 ml). Hidróxido de sodio 2M (0.309 ml, 0.617 mmoles) se añadió y la mezcla de reacción se agitó a 60°C durante 4 hr. El solvente se evaporó, después la mezcla de reacción se diluyó con agua y se neutralizó con ácido clorhídrico 2M y se extrajo con acetato de etilo. La fase orgánica se lavó con agua, se secó y se evaporó para dar el producto como un sólido incoloro (27 mg).

δH (400 MHz, D_6-DMSO). 1.36 (6H,d), 2.42 (2H, br t), 2.65-2.70 (2H, m), 3.90 (2H, s), 4.04-4.09 (2H, m), 4.88 (1H, m), 7.21 (1H, dd), 7.44 (1H, d), 7.51 (1H, d), 7,79 (1H, d), 8.09 (1H, d), 8.17 (1H,s).

EM (EA) $C_{23}H_{24}{}^{35}ClN_3O_5$ requiere 457 Encontrado 458 $[M+H]^+$.

EJEMPLO 48

Formiato de 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)-1,2,4-oxadiazol-5-il]-3-piridinacarbonitrilo



7-(5-{5-Ciano-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo (preparación 95) (224 mg, 0.471 mmoles) en diclorometano (1 ml) se trató con HCl 4M en dioxano (5 ml, 20.0 mmoles). La solución incolora se dejó a temperatura ambiente durante el fin de semana para dar un precipitado incoloro. La mezcla de reacción se concentró, se trituró con éter y se secó. El producto crudo se trató con DMSO:MeOH (1:1; 1.9 ml), la mezcla se filtró y el filtrado se purificó por PADM. El compuesto del título se obtuvo como una sal de formiato (55 mg),

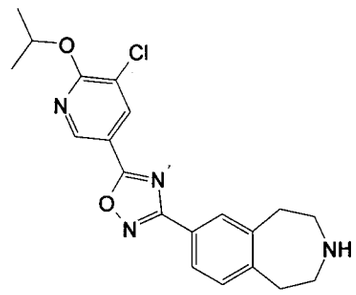
δH (400 MHz, d_6DMSO), 1.41 (6H, d), 3.07-3.20 (4H,m), 5.51 (1H, m), 7.42 (1H, d), 7.88 (1H dd), 7.91 (1H, d), 8.24 (1H, s), 8.98 (1H, d) y 9.20 (1H, d);

EM (EA) $C_{21}H_{21}N_5O_2$ requiere 375; encontrado 376$[M+H]^+$.

328

EJEMPLO 49

Clorhidrato de 7-(5-{5-Cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1*H*-3-benzazepina



7-(5-{5-Cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-carboxilato de 1,1-dimetiletilo (preparación 96) (305 mg, 0.629 mmoles) en diclorometano (2 ml) a temperatura ambiente se trató con ácido trifluoroacético (1 ml, 12.98 mmoles) y la mezcla se agitó durante 1 hr. La mezcla de reacción se concentró y el residuo se dividió entre NaOH 2M y acetato de etilo. El extracto de acetato de etilo se lavó con salmuera, se secó y se concentró a una goma incolora que se cristalizó lentamente, para dar la base libre del compuesto del título (229 mg).

Una porción de la base libre (37 mg) se disolvió en metanol (0.5 ml) y se trató con exceso de HCl en metanol (1.25M; 0.4 ml). La solución se evaporó para dar el compuesto del título como un sólido incoloro (42 mg).

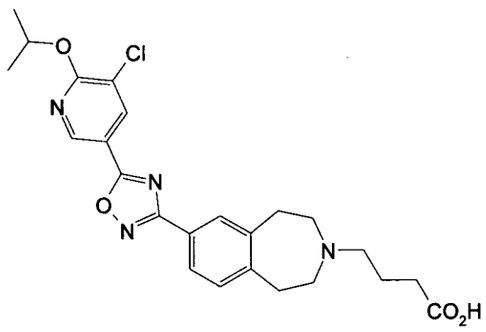
δH (400 MHz, d_6DMSO), 1.39 (6H, d), 3.21 (8H, d), 5.45 (1H, m), 7.45 (1H, d), 7.91 (1H, dd), 7.95 (1H, d), 8.55 (1H, d), 8.92 (1H, d) y 9.33 (2H, br s);

329

EM (EA) $C_{20}H_{21}{}^{35}ClN_4O_2$ requiere 384; encontrado 385 $[M+H]^+$.

EJEMPLO 50

Acido 4-[7-(5-{5-cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]butanoico



Una suspensión de 4-[7-(5-{5-cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]butanoato de etilo (preparación 97) (185 mg, 0.371 mmoles) en etanol (3 ml), se trató con hidróxido de sodio 2M (0.556 ml, 1.11 mmoles) a temperatura ambiente durante la noche para dar un precipitado incoloro. Se añadieron 1-2 ml adicionales de etanol y la temperatura se elevó a 50°C para completar la reacción. Se añadió ácido acético (0.07 ml, 1.22 mmoles) a la solución y la mezcla se concentró. El residuo oleoso resultante se trató con agua (aprox. 3 ml) después se agitó a temperatura ambiente durante 1-2 hr y se filtró. El sólido se lavó con agua, después se disolvió en metanol y el solvente se evaporó. El sólido resultante se secó durante la noche bajo vacío a aprox. 60°C para dar el compuesto del título (153 mg).

δH (400 MHz, d_6DMSO), 1.39 (6H, d), 1.69 (2H, m) 2.26 (2H, t), 2.47 (2H, t), 2.61 (4H, br s), 2.95 (4H, br m), 5.45 (1H, m), 7.34 (1H, d), 7.80-7.85 (2H, m), 8.53 (1H, d) y 8.90 (1H, d);

EM (EA) $C_{24}H_{27}{}^{35}ClN_4O_4$ requiere 470; encontrado 471 $[M+H]^+$.

Preparación de membrana para prueba de S1P1 GTPγS

Para preparaciones de membrana, todos los pasos se realizaron a 4°C. Células de hepatoma de rata que expresan establemente el receptor de S1P1 humano o células de leucemia basofílicas de rata (RBL) que expresan establemente el receptor de S1P3 humano se hicieron crecer a 80% de confluencia antes de ser cosechadas en 10 ml de solución salina regulada en su pH con fosfato (PBS) y centrifugadas a 1200 rpm durante 5 minutos. Después de remover el sobrenadante, la pastilla se re-suspendió y las células se homogeneizaron dentro de un mezclador de Waring de vidrio para 2 ráfagas de 15 seg en 200 ml de regulador de pH (HEPES 50 mM, leupeptina 1 mM, 25 μg/ml de bacitracin, EDTA 1 mM, PMSF 1 mM, pepstatina A 2 μM). El mezclador se colocó en hielo durante 5 min después de la primera ráfaga y 10-40 min después de la ráfaga inicial para dejar que la espuma se disipara. El material después se hizo girar a 500 g durante 20 min y el sobrenadante se agitó durante 36 min a 48,000 g. La pastilla se resuspendió en el mismo regulador de pH que antes pero sin PMSF y pepstatina A. El material después se forzó a través de una aguja de 0.6 mm, se llevó al volumen requerido,

331

(usualmente x4 el volumen de la pastilla de células original), se hicieron alícuotas con el mismo y se almacenó bajo congelamiento a –80°C.

Preparación de membrana alternativa para prueba de S1P1 GTPγS

Todos los pasos se realizaron a 4°C. Las células se homogeneizaron dentro de un mezclador de Waring de vidrio para 2 ráfagas de 15 seg en 200 ml de regulador de pH (HEPES 50 mM, leupeptina 1 mM, 25 μg/ml de bacitracin, EDTA 1 mM, PMSF 1 mM, pepstatina A 2 μM). El mezclador se colocó en hielo durante 5 min después de la primera ráfaga y 10-40 min después de la ráfaga inicial para dejar que la espuma se disipara. El material después se hizo girar a 500 g durante 20 min y el sobrenadante se agitó durante 36 min a 48,000 g. La pastilla se resuspendió en el mismo regulador de pH que antes pero sin PMSF y pepstatina A. El material después se forzó a través de una aguja de 0.6 mm, se llevó al volumen requerido, (usualmente x4 el volumen de la pastilla de células original), se hicieron alícuotas con el mismo y se almacenó bajo congelamiento a –80°C.

Prueba de S1P1 GTPγS

Membranas de hepatoma de rata de S1P1 humano (1.5 μg/pozo) se adhirieron a esferas (0.125 mg/pozo) de prueba de proximidad de escintilación revestidas (SPA) con aglutinina de germen de trigo (WGA) en un

regulador de pH de prueba (HEPES 20 mM, $MgCl_2$ 10 mM, NaCl 100 mM y pH adjustado a 7.4 usando KOH 5M, GDP 10 μM FAC (concentración de prueba final) y saponina 90 μg/ml FAC también se añadió).

Después de 30 minutos de pre-acoplamiento sobre hielo, la suspensión de esferas y membrana se suministró en una placa LV384-pozos de polipropileno Greiner blanca (5 μl/pozo), que contenía 0.1 μl del compuesto. 5 μl/pozo [^{35}S]-GTPγS (concentración de radioligando final de 0.5 nM) formada en regulador de pH de prueba se añadió después a placas con agonista. El cóctel de prueba final (10.1 μl) después se centrifugó a 1000 rpm durante 5 minutos, después se leyó inmediatamente en un lector Viewlux.

Todos los compuestos de prueba se disolvieron en DMSO a una concentración de 10 mM y se prepararon en 100% de DMSO usando un paso de dilución de 1 en 4 para proveer curvas de dosis-respuesta de 11 puntos. Las diluciones fueron transferidas a las placas de prueba asegurándose de que la concentración DMSO fuera constante a través de la placa para todas las pruebas.

Todos los datos se normalizaron a la media de 16 pozos de control altos y 16 bajos en cada placa. Un ajuste de curva de cuatro parámetros se aplicó después.

Método alternativo para prueba de S1P1 GTPγS

Membranas RH7777 que expresan S_1P_1 (1.5 μg/pozo) fueron

homogeneizadas al pasar a través de una aguja de 23G. Estas después se adhirieron a esferas de SPA revestidas con WGA (0.125 mg/pozo) en regulador de pH de prueba (HEPES 20 mM, $MgCl_2$ 10 mM, NaCl 100 mM y pH adjustado a 7.4 usando KOH 5M). GDP 10 μM FAC y saponina 90 μg/ml FAC también se añadieron.

Después de 30 minutos de pre-acoplamiento sobre hielo, la suspensión de esferas y membrana se suministró en una placa LV384-pozos de polipropileno Greiner blanca (5 μl/pozo), que contenía 0.1 μl del compuesto. 5 μl/pozo [^{35}S]-GTPγS (concentración de radioligando final de 0.5 nM para S_1P_1 o 0.3 nM para S_1P_3) formada en regulador de pH de prueba se añadió después a las placas. El cóctel de prueba final (10.1 μl) después se selló, se agitó en una centrífuga, después se leyó inmediatamente en un instrumento Viewlux.

Los compuestos ilustrados como ejemplo de la invención tuvieron una pCE50 > 5, muchos tuvieron una pCE50 >7. Los ejemplos 6, 7, 8, 12, 18, 19, 21 a 29, 31 a 35, 37, 39, 41, 43, 47, 48 y 50 tuvieron una pCE50 >7. Los ejemplos 7, 21, 23, 24 y 26 a 28 tuvieron una pCE50 ≥8.

Prueba de S1P3 GTPγS

Membranas de S1P3 de células de leucemia basofílicas de rata (RBL-2H3)(1.5 μg/pozo) se adhirieron a esferas de SPA revestidas con WGA (0.125 mg/pozo) en regulador de pH de prueba (HEPES 20 mM, $MgCl_2$ 3 mM,

NaCl 100 mM y pH ajustado a 7.4 usando KOH 5M), GDP 10 μM FAC y saponina 90 μg/ml FAC también se añadió).

Después de 30 minutos de pre-acoplamiento sobre hielo, la suspensión de esferas y membrana se suministró en una placa LV384-pozos de polipropileno Greiner blanca (5 μl/pozo), que contenía 0.1 μl del compuesto. 5 μl/pozo [^{35}S]-GTPγS (concentración de radioligando final de 0.5 nM) formada en regulador de pH de prueba se añadió después a placas con agonista. El cóctel de prueba final (10.1 μl) después se centrifugó a 1000 rpm durante 5 minutos, después se leyó inmediatamente en un lector Viewlux.

Todos los compuestos de prueba se disolvieron en DMSO a una concentración de 10 mM y se prepararon en 100% de DMSO usando un paso de dilución de 1 en 4 para proveer curvas de dosis-respuestas de 11 puntos. Las diluciones fueron transferidas a las placas de prueba asegurándose de que la concentración DMSO fuera constante a través de la placa para todas las pruebas.

Todos los datos se normalizaron a la media de 16 pozos de control altos y 16 bajos en cada placa. Un ajuste de curva de cuatro parámetros se aplicó después.

<u>Método alternativo para prueba de S1P3 GTPγS</u>

Membranas de RBL que expresan S_1P_3 (1.5 μg/pozo) fueron homogeneizadas al pasar a través de una aguja de 23G. Estas después se

adhirieron a esferas de SPA revestidas con WGA (0.125 mg/pozo) en regulador de pH de prueba (HEPES 20 mM, $MgCl_2$ 10 mM, NaCl 100 mM y pH ajustado a 7.4 usando KOH 5M). GDP 10 μM de FAC y saponina 90 μg/ml de FAC también se añadieron.

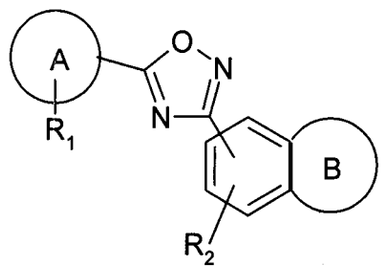
Después de 30 minutos de pre-acoplamiento sobre hielo, la suspensión de esferas y membrana se suministró en una placa LV384-pozos de polipropileno Greiner blanca (5 μl/pozo), que contenía 0.1 μl del compuesto. 5 μl/pozo [^{35}S]-GTPγS (0.5 nM para S_1P_1 o 0.3 nM para concentración de radioligando final de S_1P_3) formada en regulador de pH de prueba se añadió después a placas. El cóctel de prueba final (10.1 μl) después se selló, se agitó sobre una centrífuga, después se leyó inmediatamente en un instrumento Viewlux.

Los compuestos ilustrados como ejemplo tuvieron una pCE50 < 6, muchos tuvieron una pCE50 <5. Los ejemplos 1 a 5, 8 a 14, 16, a 22, 26, 30 a 34, 36, 37, 39 a 41, 43 a 50 tuvieron una pCE50 ≤5.

NOVEDAD DE LA INVENCION

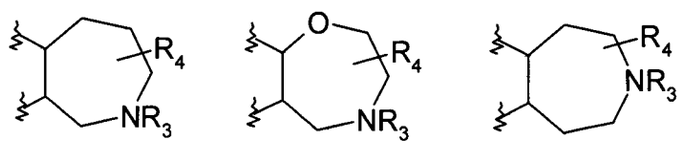
REIVINDICACIONES

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



(I)

A es fenilo o un anillo de heteroarilo de 5 ó 6 miembros; R_1 es de hasta dos sustituyentes independientemente seleccionados de halógeno, alcoxi de $C_{(1-3)}$, fluoroalquilo de $C_{(1-3)}$, ciano, fenilo opcionalmente sustituido, fluoroalcoxi de $C_{(1-3)}$, alquilo de $C_{(1-6)}$ y cicloalquilo de $C_{(3-6)}$; R_2 es hidrógeno, halógeno o alquilo de $C_{(1-4)}$; B es un anillo saturado de 7 miembros seleccionado de los siguientes:



R_3 es hidrógeno o $(CH_2)_{1-4}CO_2H$; R_4 es hidrógeno o alquilo de $C_{(1-3)}$

opcionalmente interrumpido por oxígeno.

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

3.- Un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable del mismo, en donde: A es fenilo o piridinilo; y/o R_1 es de hasta dos sustituyentes independientemente seleccionados de cloro, isopropoxi y ciano; R_2 es hidrógeno; y/o B es (b); y/o R_3 es hidrógeno o $(CH_2)_{1-4}CO_2H$; y/o R_4 es hidrógeno.

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

5.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque es seleccionado de: 7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1H-2-benzazepina; ácido [7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]acético; 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1H-2-benzazepin-7-il)-1,2,4-oxadiazol-5-il]benzonitrilo; ácido [7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]acético; ácido 4-[7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-

oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]butanoico; ácido 3-[7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]propanoico; 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1H-3-benzazepin-6-il)-1,2,4-oxadiazol-5-il]benzonitrilo; 6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1H-3-benzazepina; ácido 3-[6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]propanoico; ácido [6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]acético; 6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1H-2-benzazepina; ácido [6-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,3,4,5-tetrahidro-2H-2-benzazepin-2-il]acético; 8-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1,4-benzoxazepina; ácido 3-[8-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoico; ácido 4-[8-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]butanoico; ácido [8-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]acético; 7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1H-3-benzazepina; 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)-1,2,4-oxadiazol-5-il]benzonitrilo; 7-{5-[4-[(1-metiletil)oxi]-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-2,3,4,5-tetrahidro-1H-3-benzazepina; 7-{5-[2-(trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-2,3,4,5-tetrahidro-1H-3-benzazepina; ácido 3-[7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-

benzazepin-3-il]propanoico; ácido [7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]acético; ácido [7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]acético; ácido (7-{5-[4-[(1-metiletil)oxi]-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il)acético; ácido (7-{5-[2-(trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il)acético; ácido 4-[7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]butanoico; ácido 4-[7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]butanoico; ácido 4-(7-{5-[4-[(1-metiletil)oxi]-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il)butanoico; ácido 4-(7-{5-[2-(trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il)butanoico; 2-(Metiloxi)-5-[3-(2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)-1,2,4-oxadiazol-5-il]benzonitrilo; 9-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1,4-benzoxazepina; 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1,4-benzoxazepin-9-il)-1,2,4-oxadiazol-5-il]benzonitrilo; ácido 4-[9-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]butanoico; ácido 4-[9-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]butanoico; 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1,4-benzoxazepin-7-il)-1,2,4-oxadiazol-5-il]benzonitrilo; clorhidrato de 7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1,4-benzoxazepina; ácido 3-[7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-

1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoico; ácido 3-[7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoico; ácido 4-[7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]butanoico; ácido 4-[7-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]butanoico; 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1,4-benzoxazepin-8-il)-1,2,4-oxadiazol-5-il]benzonitrilo; ácido 4-[8-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]butanoico; ácido 5-[9-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]pentanoico; ácido [9-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]acético; ácido 3-[9-(5-{5-cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoico; ácido 3-[9-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoico; ácido 3-[9-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5H)-il]propanoico; formiato de 2-[(1-metiletil)oxi]-5-[3-(2,3,4,5-tetrahidro-1H-3-benzazepin-7-il)-1,2,4-oxadiazol-5-il]-3-piridincarbonitrilo; clorhidrato de 7-(5-{5-cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-2,3,4,5-tetrahidro-1*H*-3-benzazepina; ácido 4-[7-(5-{5-cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]butanoico; y sales farmacéuticamente aceptables de los mismos.

6.- El compuesto de conformidad con la reivindicación 1,

caracterizado además porque es clorhidrato de ácido 4-[7-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1,2,4,5-tetrahidro-3H-3-benzazepin-3-il]butanoico o una sal farmacéuticamente aceptable del mismo.

7.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque es ácido 4-[9-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-2,3-dihidro-1,4-benzoxazepin-4(5*H*)-il]butanoico o una sal farmacéuticamente aceptable del mismo.

8.- El uso de un compuesto de cualquiera de las reivindicaciones 1 a 7 para el tratamiento de condiciones o trastornos mediados por receptores de S1P1.

9.- El uso como se reclama en la reivindicación 8, 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 de isquemia-reperfusión, tumores sólidos y metástasis de tumor, enfermedades asociadas con angiogénesis, enfermedades vasculares, condiciones de dolor, enfermedades virales agudas, condiciones intestinales inflamatorias, diabetes dependiente de insulina y no dependiente de insulina.

10.- El uso como se reclama en la reivindicación 9, en donde la condición es lupus eritematoso.

11.- El uso de un compuesto de cualquiera de las reivindicaciones 1 a 7 para la fabricación de un medicamento para usarse en el tratamiento de condiciones o trastornos mediados por receptores de S1P1.

12.- El uso como se reclama en la reivindicación 11, 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 de isquemia-reperfusión, tumores sólidos y metástasis de tumor, enfermedades asociadas con angiogénesis, enfermedades vasculares, condiciones de dolor, enfermedades virales agudas, condiciones intestinales inflamatorias, diabetes dependiente de insulina y no dependiente de insulina.

13.- El uso como se reclama en la reivindicación 12, en donde la condición es lupus eritematoso.

14.- Una composición farmacéutica que comprende un compuesto de cualquiera de las reivindicaciones 1 a 7.

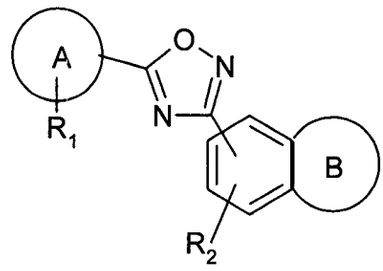
15.- Un método de tratamiento para condiciones o trastornos en mamíferos incluyendo humanos que pueden ser mediadas por los receptores de S1P1, que comprende administrar al paciente una cantidad terapéuticamente segura y efectiva de un compuesto de la fórmula (I) o una sal farmacéuticamente aceptable de los mismos.

16.- El método de tratamiento de conformidad con la reivindicación 15, caracterizado además porque la condición es lupus eritematoso.

343

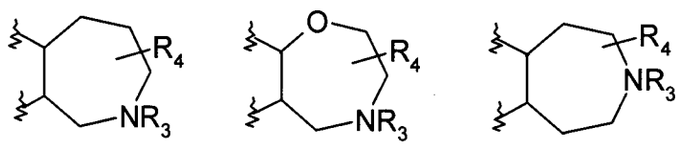
RESUMEN DE LA INVENCION

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



(I)

activos sobre 1-fosfato esfingosina (S1P) en particular útiles para tratar lupus eritematoso; A es fenilo o un anillo de heteroarilo de 5 ó 6 miembros; R_1 es de hasta dos sustituyentes independientemente seleccionados de halógeno, alcoxi de$C_{(1-3)}$, fluoroalquilo de $C_{(1-3)}$, ciano, fenilo opcionalmente sustituido, fluoroalcoxi de $C_{(1-3)}$, alquilo de $C_{(1-6)}$ y cicloalquilo de $C_{(3-6)}$; R_2 es hidrógeno, halógeno o alquilo de $C_{(1-4)}$; B es un anillo saturado de 7 miembros seleccionado de los siguientes:



(a) (b) (c)

R_3 es hidrógeno o $(CH_2)_{1-4}MCO_2H$; R_4 es hidrógeno o alquilo de $C_{(1-3)}$ opcionalmente interrumpido por oxígeno.

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.

The structure of S1P active compounds is known to be composed of an aromatic substituent, connected via a central heterocycle to a phenyl [see Figure 1 of D2]. It was suggested in the prior art to modify (in a lead compound) the positions on said phenyl ring and next to it [see Figure 1 of D3.

There was no oxadiazole type S1P active compound having the structure of 6-membered ring **fused to a 7-membered** ring known in the prior art published prior to the present priority date. Thus a skilled person would have no motivation to modify either the compounds of D1 or the lead compound of D3 in order to provide this new structural type of compounds. Furthermore the assays described in the present application confirm the pharmacological effect of the present compounds.

The new compounds, their pharmaceutical compositions and applications appear to comply with the requirements of the Article 33(3) PCT.

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.

There appears an error in the publication number of the cited prior art document on p. 2, l. 16, which should be corrected to WO2008/064337.

The independant claims 2-4 contain all the features of the independant claim 1, and should be made dependant on the later (Rule 6.4 PCT).

The cope of protection is rendered unclear by the incorporations by reference, such as on p. 27.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/067965

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/04 C07D413/14 C07D223/16 C07D267/14 C07D271/06
A61P37/00 A61P17/00 A61K31/55

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.
A	WO 2007/116866 A (ASTELLAS PHARMA INC [JP]; HARADA HIRONORI [JP]; HATTORI KAZUYUKI [JP];) 18 October 2007 (2007-10-18) cited in the application	
A	& EP 2 003 132 A (ASTELLAS PHARMA INC [JP]) 17 December 2008 (2008-12-17) claim 1	

-/--

[X] Further documents are listed in the continuation of Box C. [X] 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	Date of mailing of the international search report
24 February 2009	06/03/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Fax: (+31–70) 340–3016	Skulj, Primoz

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/067965

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	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; table 1	
A	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	
P,A	WO 2008/064337 A (UNIV VIRGINIA [US]; LYNCH KEVIN R [US]; MACDONALD TIMOTHY L [US]) 29 May 2008 (2008-05-29) cited in the application claim 1; figure 6	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/067965

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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
WO 2008064337 A	29-05-2008	NONE	

PATENT COOPERATION TREATY

348

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

Received
09 MAR 2009

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

(PCT Rule 44.1)

Applicant's or agent's file reference JEG/PB62784	Date of mailing *(day/month/year)* 06/03/2009
International application No. PCT/EP2008/067965	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant GLAXO GROUP LIMITED	International filing date *(day/month/year)* 19/12/2008

1. [x] 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, Fascimile 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 90*bis*.1 and 90*bis*.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	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Jaap Hurenkamp

NOTES TO FORM PCT/ISA/220

344

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

350

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1–10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1*bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion 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 (Rule 43*bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

PATENT COOPERATION TREATY

PCT

351

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
JEG/PB62784		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2008/067965	19/12/2008	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.

[X] 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:

[X] 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 43.6*bis*(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

[X] 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

[X] 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

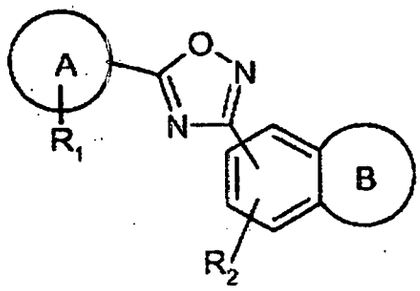
[ ] as selected by this Authority, because this figure better characterizes the invention

b. [ ] none of the figures is to be published with the abstract

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

Abstract

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



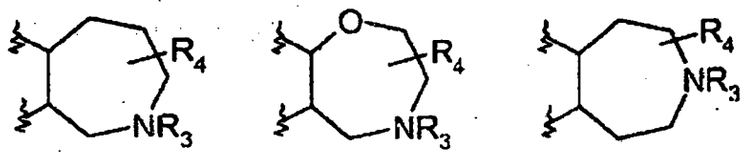
(I)

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

R_1 is up to two substituents independently selected from halogen, $C_{(1-3)}$alkoxy, $C_{(1-3)}$fluoroalkyl, cyano, optionally substituted phenyl, $C_{(1-3)}$fluoroalkoxy, $C_{(1-6)}$alkyl and $C_{(3-6)}$cycloalkyl;

R_2 is hydrogen, halogen or $C_{(1-4)}$alkyl;

B is a 7 membered saturated ring selected from the following:



(a) (b) (c)

R_3 is hydrogen or $(CH_2)_{1-4}CO_2H$;

R_4 is hydrogen or $C_{(1-3)}$alkyl optionally interrupted by oxygen;

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/067965

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D413/04 C07D413/14 C07D223/16 C07D267/14 C07D271/06
A61P37/00 A61P17/00 A61K31/55

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.
A	WO 2007/116866 A (ASTELLAS PHARMA INC [JP]; HARADA HIRONORI [JP]; HATTORI KAZUYUKI [JP];) 18 October 2007 (2007-10-18) cited in the application	
A	& EP 2 003 132 A (ASTELLAS PHARMA INC [JP]) 17 December 2008 (2008-12-17) claim 1	

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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	Date of mailing of the international search report
24 February 2009	06/03/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Fax: (+31–70) 340–3016	Skulj, Primoz

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	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; table 1	
A	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	
P,A	WO 2008/064337 A (UNIV VIRGINIA [US]; LYNCH KEVIN R [US]; MACDONALD TIMOTHY L [US]) 29 May 2008 (2008-05-29) cited in the application claim 1; figure 6	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/067965

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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
WO 2008064337 A	29-05-2008	NONE	

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.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.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2008/067965	19.12.2008	21.12.2007

International Patent Classification (IPC) or both national classification and IPC
INV. C07D413/04 C07D413/14 C07D223/16 C07D267/14 C07D271/06 A61P37/00 A61P17/00 A61K31/55

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 43*bis*.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 notifed the International Bureau under Rule 66.1*bis*(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:	Date of completion of this opinion	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	see form PCT/ISA/210	Skulj, Primoz Telephone No. +31 70 340-1960

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/EP2008/067965

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	1-16
	No:	Claims	/
Inventive step (IS)	Yes:	Claims	1-16
	No:	Claims	/
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	/

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

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: WO 2007/116866 A cited in the application
D2: VACHAL PETR ET AL, BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 15 JUL 2006, vol. 16, no. 14, 15 July 2006, pages 3684-3687, XP002515397 ISSN: 0960-894X
D3: YAN LIN ET AL, 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 sphinghosine-1-phosphate (S1P).

1 Note

Claims 15,16 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 and Inventive Step (A.33(2) and 33(3) PCT)

The claimed compounds, their pharmaceutical compositions and uses are new in the sense of Article 33(2) PCT.

The closest prior art to the compounds of the present invention is D1 which discloses S1P active compounds having the following structure: a bicyclic aromatic substituent (made of a 6-membered ring **fused to either a 5- or a 6-membered ring**), connected via the oxadiazole to phenyl or pyridyl. [see claim 1]. In the instant compounds, the bicyclic aromatic substituent is a 6-membered ring **fused to a 7-membered** ring. The effect of this modification is not given.

360

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-074455- -00000-0000

Fecha: 2010-06-21 16:58:04 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 359

PATENTE DE INVENCIÓN ☐ **MODELO DE U**

- ☐ 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 INVENCIÓN 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 ☐

361

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

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

REFERENCIA	Radicación No.	10 074455
	Solicitud internacional	PCT/EP2008/067965
	Fecha inicio fase nacional	21/07/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	10534

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular 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

362

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

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

REFERENCIA	Radicación No.	10 074455
	Solicitud internacional	PCT/EP2008/067965
	Fecha inicio fase nacional	21/07/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	10535

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 titulo primero de la Circular Única N° 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