



CSA045277

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO



Organizacion y
Digitalizacion CSA Ltda

Industria y Comercio
SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISION DE NUEVAS CREACIONES

09-62875

SOLICITUD DE PATENTE DE

INVENCION

JLO DERIVADOS INDOLE COMO AGONISTAS DEL RECEPTOR S1P1

JICITANTE GLAXO GROUP LIMITED

ECCION Glaxo Wellcome House, Berkeley Avenue, Greenford,
dlesex UB6 ONN Inglaterra

ORDERADO CARLOS R OLARTE

BOGOTA 17 de Junio de 2009

OLARTE RAISBECK

OLARTE RAISBECK MOURE & CASTRO, L.P.A.



SUPLINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-062875- -00000-0000

Fecha: 2009-06-17 17:18:15

Dep. 2020 NUECREACION

Lra. 11 PATENTEIYII

Eve: 378 FASENACIONALI

Act. 411 PRESENTACION

Folios: 296

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD PATENTE PCT

ENTRADA EN FASE NACIONAL

P2009/000105

SOLICITUD DE:

1



Patente de Invención.



Patente de Modelo de Utilidad.



Capítulo I.



Capítulo II.

2

SOLICITANTE
(71)

Nombre: GLAXO GROUP LIMITED

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

Nacionalidad o Domicilio: Británica

Lugar de Constitución: Gran Bretaña

Teléfono: _____

Fax: _____

E-mail: _____

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

REPRESENTANTE
O APODERADO

Nombre: CARLOS R. OLARTE

Dirección: World Trade Center Torre A,
Calle 100 No. 8A-37 Piso 10

Teléfono: 601-7700 Fax: 601-7799

E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número 79.782.747Bta
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/EP2007/064185

Fecha

Diciembre 19, 2007

Publicación Internacional No. WO 2008/074821

Fecha

Junio 26, 2008

6

Título (54) DERIVADOS INDOLE COMO AGONISTAS DEL RECEPTOR S1P1

Clasificación Internacional (51) C07D 413/04, C07D 413/14, A61K 31/405, A61P 37/00.

Prioridad
SI ☒ NO ☐

(33) País de Origen

GB

GB

(32) Fecha

Diciembre 21 2006

Abril 19, 2007

(31) Número de Solicitud

0625647.3

0707615.1

9

Comprobante de pago No. 09-44.582

Fecha Junio 16 de 2009



ANEXOS

2



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



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



Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 07-007.709.



Documento de cesión del inventor al solicitante o a su causante.



Declaraciones



Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).



Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).



Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).



Traducción del examen preliminar internacional efectuado por la IPEA.



De ser el caso, copia del contrato de acceso.



De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.



De ser el caso, certificado de depósito del material biológico.



Arte final 12 x 12.



De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.



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



Otros. Búsqueda Internacional



FIGURA CARACTERÍSTICA:



Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA:

C.C. 79.482.747 Btá T.P. 74.295

LISTA DE INVENTORES PCT/EP2007/064185**MAHMOOD AHMED**

Biopolis at One-North
The Helios Block #03-01/02
11Biopolis Way
138667 Singapore
Nacionalidad: Británica

JAMES MYATT

New Frontiers Science Park South
Third Avenue
Harlow, Essex, CM19 5AW
Reino Unido
Nacionalidad: Británica

DAVID NORTON

New Frontiers Science Park South
Third Avenue
Harlow, Essex, CM19 5AW
Reino Unido
Nacionalidad: Británica

DEAN ANDREW RIVERS

Biopolis at One-North
The Helios Block #03-01/02
11Biopolis Way
138667 Singapore
Nacionalidad: Británica

4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-062875- -00000-0000

Fecha: 2009-06-17 17:18:15

Dep. 2020 NUECREACION I
Eje: 378 FASE NACIONAL I

Tra. 11 PATENTIFIJII

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CIBO OFICIAL DE CAJA : 09 - 44,582
CHA : JUNIO 16 DE 2009

***** CONSIGNACION *****

POSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	105800155	16/06/2009	6,975,000.00

***** CONCEPTO *****

NT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	540,000.00
	TOTAL :	\$ 540,000.00

N: QUINIENTOS CUARENTA MIL PESOS

SPONSABLE : _____

CIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

APOSTILLA EN PODER DE REPRESENTACIÓN DE

GLAXO GROUP LIMITED

PODER DE REPRESENTACION

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

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

APOSTILLA

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

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

CERTIFICADO

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

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

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

Marlen Neira C

Marlen Neira C

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

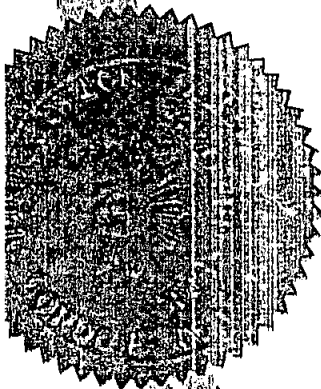
C E R T I F I C O:

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

QUE el citado Señor Don **PETER JOHN GIDDINGS** está debidamente 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 trece de agosto del año dos mil tres.



JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra



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ATTESTATION

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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

This public document / Le present acte public

- 2 It has been signed by **James Kenneth Milligan**
a été signé par

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

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

Certified/Atteste

- 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 Étrangères et du Commonwealth

- 8 Number/sous No **G229474**

- 9 Stamp
timbre

10 Signature **J. Kenneth**



11th 5 13/5/03 15 1 1111

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

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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

www.olarteraisbeck.com

Power of Attorney

The undersigned,

domiciled in

Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, GB

by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana**

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

Poder

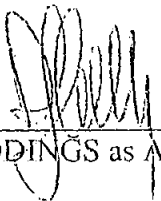
El suscrito,

domiciliado en

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

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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) and (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 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

in relation to international application No. PCT/EP2007/064185

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

- (i) transfer of entitlement from inventors **Mahmood AHMED, James MYATT, David NORTON and Dean Andrew RIVERS** to GlaxoSmithKline Services Unlimited by way of employment contract
- (ii) an assignment from GlaxoSmithKline Services Unlimited to Glaxo Group Limited dated 7 February 2008

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

Form PCT/RO/101 (declaration sheet (ii)) (March 2001; reprint January 2003)

See Notes to the request form

10

Box No. VIII(iii) DECLARATION: ENTITLEMENT TO CLAIM PRIORITY

The declaration must conform to the standardized wording provided for in Section 213; see Notes to Boxes Nos. VIII, VIII(i) and (v) (in general) and the specific Notes to Box No. VIII(iii) and 51bis.1(a)(iii)

Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)):

in relation to international application No. PCT/EP2007/064185

GLAXO GROUP LIMITED is entitled to claim priority of earlier application Nos. 0625647.3; and 0707615.1 filed in the United Kingdom by virtue of the following:

- (i) transfer of entitlement from inventors **Mahmood AHMED, James MYATT, David NORTON and Dean Andrew RIVERS** to GlaxoSmithKline Services Unlimited by way of employment contract
- (ii) an assignment from GlaxoSmithKline Services Unlimited to Glaxo Group Limited dated 7 February 2008

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

Form PCT/RO/101 (declaration sheet (iii)) (March 2001; reprint January 2003)

See Notes to the request form

Box No. VIII(iv) DECLARATION: INVENTORSHIP (only for the purposes of the designation of the United States of America).
 The declaration must conform to the following standardized wording provided for in Section 214; see Notes to Boxes Nos. VIII, VIII(I) to (v) (in general) and the specific Notes to Box No. VIII (iv). If this Box is not used, this sheet should not be included in the request.

Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv))

for the purposes of the designation of the United States of America:

I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought.

This declaration is directed to the international application of which it forms a part (if filing declaration with application).

This application is directed to international application No. PCT/EP2007/064185 (if furnishing declaration pursuant to Rule 26ter).

I hereby declare that my residence, mailing address, and citizenship are as stated next to my name.

I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Application," by application number, country or Member of the World Trade Organization, day, month and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.

Prior Applications: _____

I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. §1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name: Mahmood AHMED

Residence: Singapore
 (city and either US state, if applicable, or country)

Mailing Address: GlaxoSmithKline, Five Moore Drive, P O Box 13398, Research Triangle Park, North Carolina 27709

Citizenship: British

Inventor's Signature: 
 (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent.)

Date: 30 JANUARY 2008
 (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)

Name: James MYATT

Residence: Harlow, Essex, United Kingdom
 (city and either US state, if applicable, or country)

Mailing Address: GlaxoSmithKline, Five Moore Drive, P O Box 13398, Research Triangle Park, North Carolina 27709

Citizenship: British

Inventor's Signature: _____
 (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent.)

Date: _____
 (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)

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

12

Box No. VIII(iv) DECLARATION: INVENTORSHIP (only for the purposes of the designation of the United States of America).
 The declaration must conform to the following standardized wording provided for in Section 214; see Notes to Boxes Nos. VIII, VIII(I) to (v) (in general) and the specific Notes to Box No. VIII (iv). If this Box is not used, this sheet should not be included in the request.

**Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv))
 for the purposes of the designation of the United States of America:**

I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought.

This declaration is directed to the international application of which it forms a part (if filing declaration with application).

This application is directed to international application No. PCT/EP2007/064185 (if furnishing declaration pursuant to Rule 26ter).

I hereby declare that my residence, mailing address, and citizenship are as stated next to my name.

I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Application," by application number, country or Member of the World Trade Organization, day, month and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.

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I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. §1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name: Mahmood AHMED

Residence: Singapore
 (city and either US state, if applicable, or country)

Mailing Address: GlaxoSmithKline, Five Moore Drive, P O Box 13398, Research Triangle Park, North Carolina 27709

Citizenship: British

Inventor's Signature: _____
 (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent.)

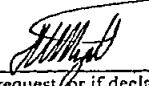
Date: _____
 (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)

Name: James MYATT

Residence: Harlow, Essex, United Kingdom
 (city and either US state, if applicable, or country)

Mailing Address: GlaxoSmithKline, Five Moore Drive, P O Box 13398, Research Triangle Park, North Carolina 27709

Citizenship: British

Inventor's Signature:  _____
 (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent.)

Date: 06/02/08
 (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)

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

13

Continuation of Box No. VIII(i) to (v) Declaration

If the space is insufficient in any of Boxes Nos. VIII(I) to (v) to furnish all the informatino, including in the case where more than two inventors are to be named in Box No. VIII (iv), in such case, write "Continuation of Box No. VIII " (indicate the item number of the Box) and furnish the information in the same manner as required for the purposes of the Box in which the space was insufficient. If additional space is needed in respect of two or more declarations, a separate continuation box must be used for each such declaration. If this Box is not used, this sheet should not be included in the request.

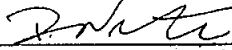
Name: David NORTON

Residence: Harlow, Essex, United Kingdom

(city and either US state, if applicable, or country)

Mailing Address: GlaxoSmithKline, Five Moore Drive, P O Box 13398, Research Triangle Park, North Carolina 27709

Citizenship: British

Inventor's Signature: 

(if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent.)

Date: 5th February 2008

(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)

Name: Dean Andrew RIVERS

Residence: Singapore

(city and either US state, if applicable, or country)

Mailing Address: GlaxoSmithKline, Five Moore Drive, P O Box 13398, Research Triangle Park, North Carolina 27709

Citizenship: British

Inventor's Signature: _____

(if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent.)

Date: _____

(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)

M

Continuation of Box No. VIII(i) to (v) Declaration

If the space is insufficient in any of Boxes Nos. VIII(i) to (v) to furnish all the information, including in the case where more than two inventors are to be named in Box No. VIII (iv), in such case, write "Continuation of Box No. VIII " (indicate the item number of the Box) and furnish the information in the same manner as required for the purposes of the Box in which the space was insufficient. If additional space is needed in respect of two or more declarations, a separate continuation box must be used for each such declaration. If this Box is not used, this sheet should not be included in the request.

Name: David NORTON

Residence: Harlow, Essex, United Kingdom

(city and either US state, if applicable, or country)

Mailing Address: GlaxoSmithKline, Five Moore Drive, P O Box 13398, Research Triangle Park, North Carolina 27709

Citizenship: British

Inventor's Signature: _____

(if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent.)

Date: _____

(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)

Name: Dean Andrew RIVERS

Residence: Singapore

(city and either US state, if applicable, or country)

Mailing Address: GlaxoSmithKline, Five Moore Drive, P O Box 13398, Research Triangle Park, North Carolina 27709

Citizenship: British

Inventor's Signature: D. MM

(if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent.)

Date: 30 JANUARY 2008

(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
26 June 2008 (26.06.2008)

PCT

(10) International Publication Number
WO 2008/074821 A1

(51) International Patent Classification:

C07D 413/04 (2006.01) A61K 31/405 (2006.01)
C07D 413/14 (2006.01) A61P 37/00 (2006.01)

(21) International Application Number:

PCT/EP2007/064185

(22) International Filing Date:

19 December 2007 (19.12.2007)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

0625647.3 21 December 2006 (21.12.2006) GB
0707615.1 19 April 2007 (19.04.2007) GB

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

(72) Inventors; and

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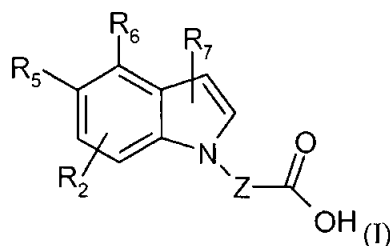
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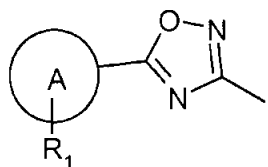
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

[Continued on next page]

(54) Title: INDOLE DERIVATIVES AS 51P1 RECEPTOR AGONISTS



(57) Abstract: The invention relates to compounds of formula (I) wherein one of R₅ and R₆ is hydrogen or R₂ and the other is (a) processes for their preparation, pharmaceutical compositions containing them and their use in the treatment of conditions or disorders which are mediated via the 51P1 receptor.





— of inventorship (Rule 4.17(iv))

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INDOLE DERIVATIVES AS S1P1 RECEPTOR AGONISTS

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

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

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

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

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

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

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

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

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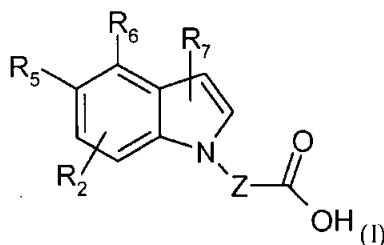
Hence, there is a need for S1P1 receptor agonist compounds with selectivity over S1P3 which might be expected to show a reduced tendency to induce bradycardia.

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

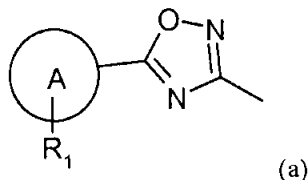
The following patent application describes indole-oxadiazole derivatives as antipicornaviral agents: WO96/009822. The following patent applications describe
15 indole-carboxylic acid derivatives as leukotriene receptor antagonists, pesticides and agrochemical fungicides respectively: WO06/090817, EP 0 439 785 and DE 39 39 238.

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

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



25 wherein
one of R₅ and R₆ is hydrogen or R₂ and the other is (a)



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

20

R₁ is hydrogen or up to three substituents independently selected from halogen, C₍₁₋₆₎alkyl, C₍₃₋₆₎cycloalkyl, C₍₁₋₆₎alkoxy, C₍₃₋₆₎cycloalkyloxy, trifluoromethoxy, difluoromethoxy, trifluoromethyl, cyano, nitro, optionally substituted piperidine, optionally substituted pyrrolidine, optionally substituted phenyl and optionally substituted 5 or 6 membered heteroaryl rings;
when R₁ is phenyl, piperidine, pyrrolidine or a 5 or 6 membered heteroaryl ring it may be substituted by up to three substituents selected from halogen, C₍₁₋₆₎alkyl, C₍₁₋₆₎alkoxy, trifluoromethoxy, difluoromethoxy, C₍₃₋₆₎cycloalkyl, trifluoromethyl and cyano;
R₂ is hydrogen or up to three substituents independently selected from halogen, C₍₁₋₄₎alkyl, C₍₁₋₄₎alkoxy, trifluoromethoxy, difluoromethoxy, trifluoromethyl and cyano;
R₇ is hydrogen or halogen;
Z is C₍₁₋₄₎alkyl which is optionally interrupted by N or O and is optionally substituted by halogen or methyl.

15 In one embodiment, when A is phenyl or pyridyl R₁ is two substituents at the para and meta positions on A relative to the oxadiazole ring.

In one embodiment, when A is thienyl R₁ is two substituents at the 4- and 5-positions.

20

In one embodiment of the invention,
R₅ is hydrogen and R₆ is (a); and/or
A is thienyl, pyridyl or phenyl; and/or
R₁ is up to three substituents selected from halogen, C₍₁₋₆₎alkoxy, or trifluoromethyl, optionally substituted phenyl, optionally substituted cyclohexyl, cyano, trifluoromethoxy, optionally substituted piperidine, optionally substituted pyrrolidine, C₍₁₋₆₎alkyl and NO₂; and/or
R₂ is hydrogen; and/or
R₇ is hydrogen or halogen; and/or
30 Z is C₍₁₋₄₎alkyl which is optionally interrupted by N or O and is optionally substituted by fluoro or methyl.

In one embodiment of the invention,
R₅ is hydrogen and R₆ is (a); and/or
35 A is pyridyl or phenyl; and/or

21

R₁ is up to two substituents selected from halogen, C₁₋₆alkoxy, or trifluoromethyl, optionally substituted phenyl, optionally substituted cyclohexyl, cyano, trifluoromethoxy, optionally substituted piperidine, optionally substituted pyrrolidine, C₁₋₆alkyl and NO₂; and/or

- 5 R₂ is hydrogen; and/or
R₇ is hydrogen, chloro or bromo; and/or
Z is unsubstituted C₍₂₋₃₎alkyl.

In one embodiment of the invention,

- 10 R₅ is hydrogen and R₆ is (a); and/or
A is pyridyl or phenyl; and/or
R₁ is up to two substituents selected from chloro, bromo, methoxy, propoxy, isopropoxy, trifluoromethyl, halo substituted phenyl, phenyl, cyclohexyl, cyano, trifluoromethoxy, piperidine, pyrrolidine, ethyl or NO₂; and/or
15 R₂ is hydrogen; and/or
R₇ is hydrogen, chloro or bromo; and/or
Z is unsubstituted C₍₂₋₃₎alkyl.

In one embodiment of the invention,

- 20 R₅ is hydrogen and R₆ is (a); and/or
A is pyridyl or phenyl; and/or
R₁ is up to two substituents selected from chloro, isopropoxy and cyano; and/or
R₂ is hydrogen; and/or
R₇ is hydrogen; and/or
25 Z is unsubstituted C₍₂₋₃₎alkyl.

In one embodiment of the invention,

- R₅ is (a) and R₆ is hydrogen.
A is optionally substituted thiophene or phenyl; and/or
30 R₁ is hydrogen, halogen, C₁₋₄alkoxy, or trifluoromethyl; and/or
R₂ is hydrogen; and/or
Z is ethylene.

In another embodiment of the invention,

- 35 R₅ is (a) and R₆ is hydrogen; and/or
A is thiophene substituted by phenyl; and/or

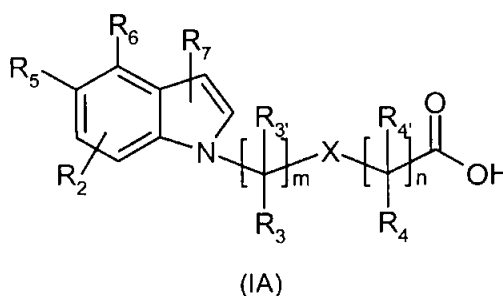
R_1 is hydrogen, halogen, C_{1-4} alkoxy, or trifluoromethyl; and/or

R_2 is hydrogen; and/or

Z is ethylene.

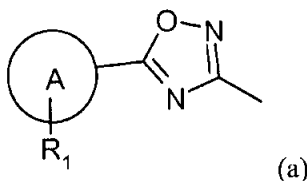
- 5 When R_1 is phenyl or a 5 or 6 membered heteroaryl ring it may be substituted by up to three substituents selected from halogen, $C_{(1-4)}$ alkyl, $C_{(1-4)}$ alkoxy, trifluoromethoxy, difluoromethoxy, trifluoromethyl and cyano.

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



wherein:

- 15 one of R_5 and R_6 is hydrogen or R_2 and the other is (a)



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

- 20 R_1 is hydrogen or up to three substituents independently selected from halogen, $C_{(1-4)}$ alkyl, $C_{(1-4)}$ alkoxy, trifluoromethoxy, difluoromethoxy, trifluoromethyl, cyano, optionally substituted phenyl and optionally substituted 5 or 6 membered heteroaryl rings;

R_2 is hydrogen or up to three substituents independently selected from halogen, $C_{(1-4)}$ alkyl, $C_{(1-4)}$ alkoxy, trifluoromethoxy, difluoromethoxy, trifluoromethyl and cyano;

- 25 R_3 , R_3' , R_4 and R_4' are each independently selected from hydrogen, halogen and methyl;

R_7 is hydrogen or halogen;

23

X is NH optionally substituted by methyl, O, CH₂ optionally substituted by fluoro or methyl, or a direct bond;

m is 0-2; and

n is 0-4.

5

When R₁ is phenyl or a 5 or 6 membered heteroaryl ring it may be substituted by up to three substituents selected from halogen, C₍₁₋₄₎alkyl, C₍₁₋₄₎alkoxy, trifluoromethoxy, difluoromethoxy, trifluoromethyl and cyano.

- 10 When X is NH it may be substituted by methyl.
When X is CH₂ it may be substituted by fluoro or methyl.

In one embodiment of the invention,

A is optionally substituted thiophene or phenyl;

- 15 R₁ is hydrogen, halogen, C₁₋₄alkoxy, or trifluoromethyl;

R₂, R₃ and R₄ are each hydrogen;

X is a direct bond;

m is 2; and

n is 0.

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In another embodiment of the invention,

A is thiophene substituted by phenyl;

R₁ is hydrogen, halogen, C₁₋₄alkoxy, or trifluoromethyl;

R₂, R₃ and R₄ are each hydrogen;

- 25 X is a direct bond;

m is 2; and

n is 0

- 30 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.

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24

Suitable C₍₃₋₆₎cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

5 Suitable C₍₃₋₆₎cycloalkyloxy groups include cyclopropoxy, cyclobutoxy, cyclopentoxy and cyclohexyloxy.

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).

10

The term "heteroaryl" represents an unsaturated ring which comprises one or more heteroatoms. When the term heteroaryl represents a 5 membered group it contains a heteroatom selected from O, N or S and may optionally contain a further 1 to 3 nitrogen atoms. When heteroaryl represents a 6-membered group it contains from 1 to 3 nitrogen atoms. Examples of such 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.

20 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.

30 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.

Suitable compounds of the invention are:

35 3-(5-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1*H*-indol-1-yl)propanoic acid

28

- 3-[5-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]propanoic acid
- 3-[3-Chloro-5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]propanoic acid
- 5 3-(3-Chloro-5-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1*H*-indol-1-yl)propanoic acid
- 10 3-(4-{5-[4-Phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1*H*-indol-1-yl)propanoic acid
- 3-[4-(5-{3-Chloro-4-[(trifluoromethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]propanoic acid
- 15 3-[4-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]propanoic acid
- 3-[4-(5-{5-Chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]propanoic acid
- 20 3-[5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]propanoic acid
- 25 (5-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1*H*-indol-1-yl)acetic acid
- 3-[3-bromo-5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]propanoic acid
- 30 5-[5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]pentanoic acid
- 4-[5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]butanoic acid
- 35

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- 4-[5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]butanoic acid
- (2S)-3-[5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]-2-methylpropanoic acid
- 5
- 2,2-dimethyl-3-(5-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid
- 10
- 3-[5-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]-2,2,3-trifluoropropanoic acid
- 4-[4-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]butanoic acid
- 15
- 3-[5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoic acid
- 3-[4-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoic acid
- 20
- 3-(4-{5-[2-(trifluoromethyl)-4-biphenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid
- 25
- 3-(4-{5-[4-cyclohexyl-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid
- 3-(4-{5-[4-[(1-methylethyl)oxy]-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid
- 30
- [4-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]acetic acid
- [4-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]acetic acid
- 35

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- 3-(4-{5-[2'-fluoro-2-(trifluoromethyl)-4-biphenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid
- 4-[4-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]butanoic acid
- 5
- 4-[4-(5-{3-chloro-4-[(trifluoromethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]butanoic acid
- 10
- 4-[4-(5-{5-chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]butanoic acid
- 4-(4-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)butanoic acid
- 15
- 4-(4-{5-[2-(trifluoromethyl)-4-biphenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)butanoic acid
- 3-(4-{5-[4-(methyloxy)-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid
- 20
- 4-{4-[5-(3-cyano-4-[(1R)-1-methylpropyl]oxy)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl}butanoic acid
- 25
- 4-{4-[5-(3-cyano-4-[(1S)-1-methylpropyl]oxy)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl}butanoic acid
- 3-(4-{5-[3-ethyl-4-(1-piperidinyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid
- 30
- 3-{4-[5-(4-cyclohexyl-3-ethylphenyl)-1,2,4-oxadiazol-3-yl]-1H-indol-1-yl}propanoic acid
- 3-(4-{5-[5-chloro-6-(1-pyrrolidinyl)-3-pyridinyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid
- 35
- 4-[4-(5-{3-bromo-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]butanoic acid
- 4-(4-{5-[3-chloro-4-(2-methylpropyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)butanoic acid
- 40

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- 3-(4-{5-[4-(2-methylpropyl)-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid
- 5 4-(4-{5-[3-cyano-4-(2-methylpropyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)butanoic acid
- 4-{4-[5-(2-cyano-4-biphenyl)-1,2,4-oxadiazol-3-yl]-1H-indol-1-yl}butanoic acid
- 10 3-(3-Chloro-4-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid
- 3-[3-chloro-5-(5-{3-chloro-4-[(trifluoromethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoic acid
- 15 3-(3-chloro-5-{5-[3-chloro-4-(propyloxy)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid
- 3-(3-chloro-5-{5-[3-chloro-4-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid
- 20 3-(3-chloro-5-{5-[4-(methyloxy)-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid
- 3-(3-chloro-5-{5-[3-chloro-4-(ethyloxy)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid
- 25 3-[3-chloro-5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl]-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoic acid
- 30 3-(3-chloro-5-{5-[4-nitro-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid
- 3-[3-chloro-5-(5-{4-chloro-3-[(1-methylethyl)oxy]phenyl]-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoic acid
- 35 3-(3-chloro-5-{5-[6-(methyloxy)-3-biphenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid



3-(5-{5-[6-(trifluoromethyl)-3-biphenyl]-1,2,4-oxadiazol-3-yl}-1*H*-indol-1-yl)propanoic acid

5 3-{5-[5-(4-phenyl-2-thienyl)-1,2,4-oxadiazol-3-yl]-1*H*-indol-1-yl}propanoic acid

3-{3-chloro-5-[5-(4-cyclohexylphenyl)-1,2,4-oxadiazol-3-yl]-1*H*-indol-1-yl}propanoic acid

10 3-(3-chloro-5-{5-[6-(4-fluorophenyl)-3-pyridinyl]-1,2,4-oxadiazol-3-yl}-1*H*-indol-1-yl)propanoic acid

3-(3-chloro-5-{5-[6-(4-fluorophenyl)-3-pyridinyl]-1,2,4-oxadiazol-3-yl}-1*H*-indol-1-yl)propanoic acid

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or pharmaceutically acceptable salts thereof.

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

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

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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.

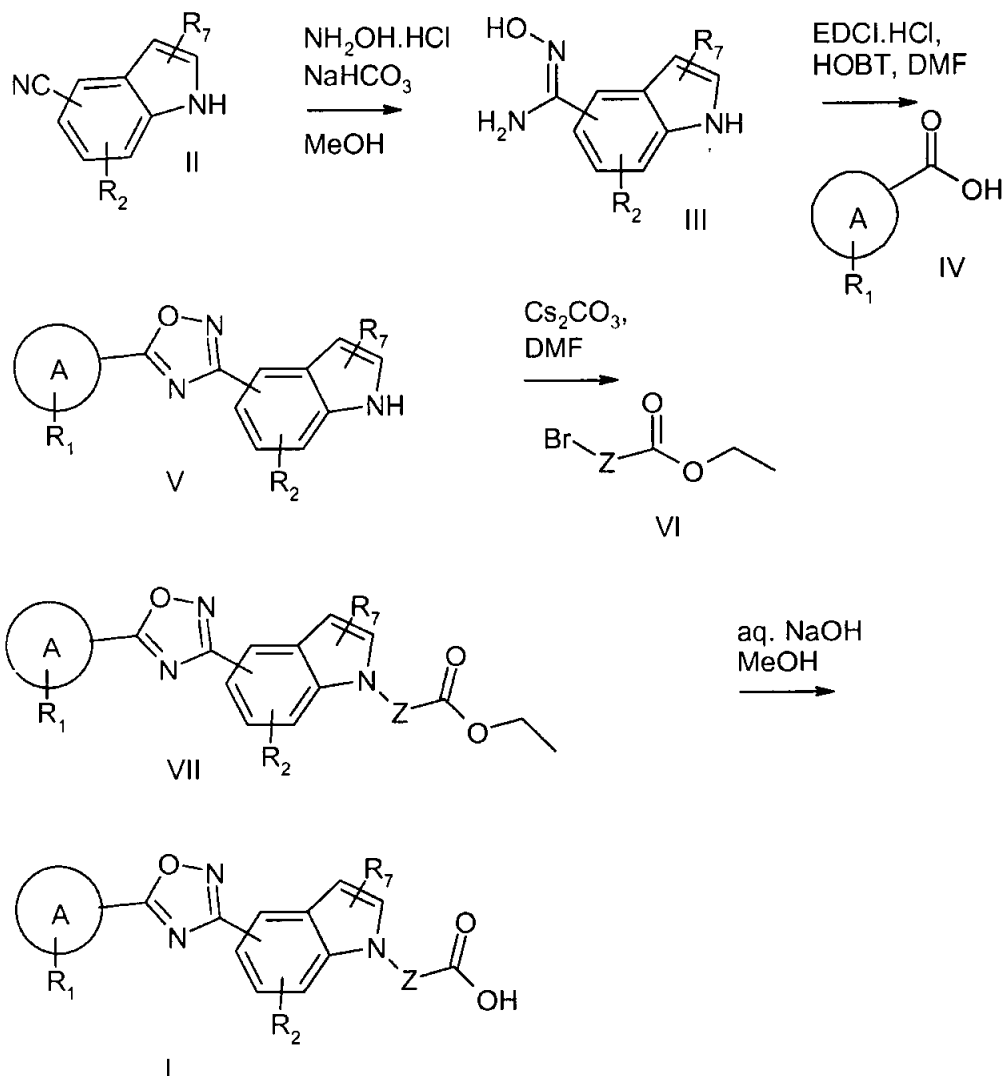
Salts may also be formed from basic ion exchange resins, for example polyamine resins. When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, ethanedisulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, pantoic, pantothenic, phosphoric, propionic, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like.

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).

In a further aspect, this invention provides processes for the preparation of a compound of formula (I). In one aspect the compound of formula (I) can be prepared by the process in Scheme I where A, Z, R₁, R₂, R₇ are as defined for formula (I)..

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Scheme I

The first step of the process (II to III) is carried out in a suitable solvent, such as methanol or ethanol and is heated to a temperature such as 50-80 °C. In the second

5 step of the process (III to V) suitable reagents include EDCI.HCl and HOBT in a solvent such as DMF at a temperature between room temperature and 90 °C or alternatively PyBOP in DMF. Alternatively (III) may be converted to (V) by treatment with the carboxylic ester of (IV) and sodium ethoxide in ethanol in a microwave

10 reaction at a temperature such as 120 °C. In the third step (V to VII) a base such as cesium carbonate or alternatively potassium carbonate is used and the reaction may be heated either conventionally or using a microwave reactor to a temperature such as 140 °C. The fourth step of the process (VII to I) is carried out in a suitable solvent

32

such as methanol or alternatively ethanol and may be carried out at either room temperature or elevated temperature such as 40 or 50 °C.

Compounds of formula (IV) are either commercially available, may be prepared by using methods described in the literature or can be prepared as described in the experimental section. Bromides of formula (VI) are either commercially available or may be prepared by using methods described in the literature or using the methods disclosed.

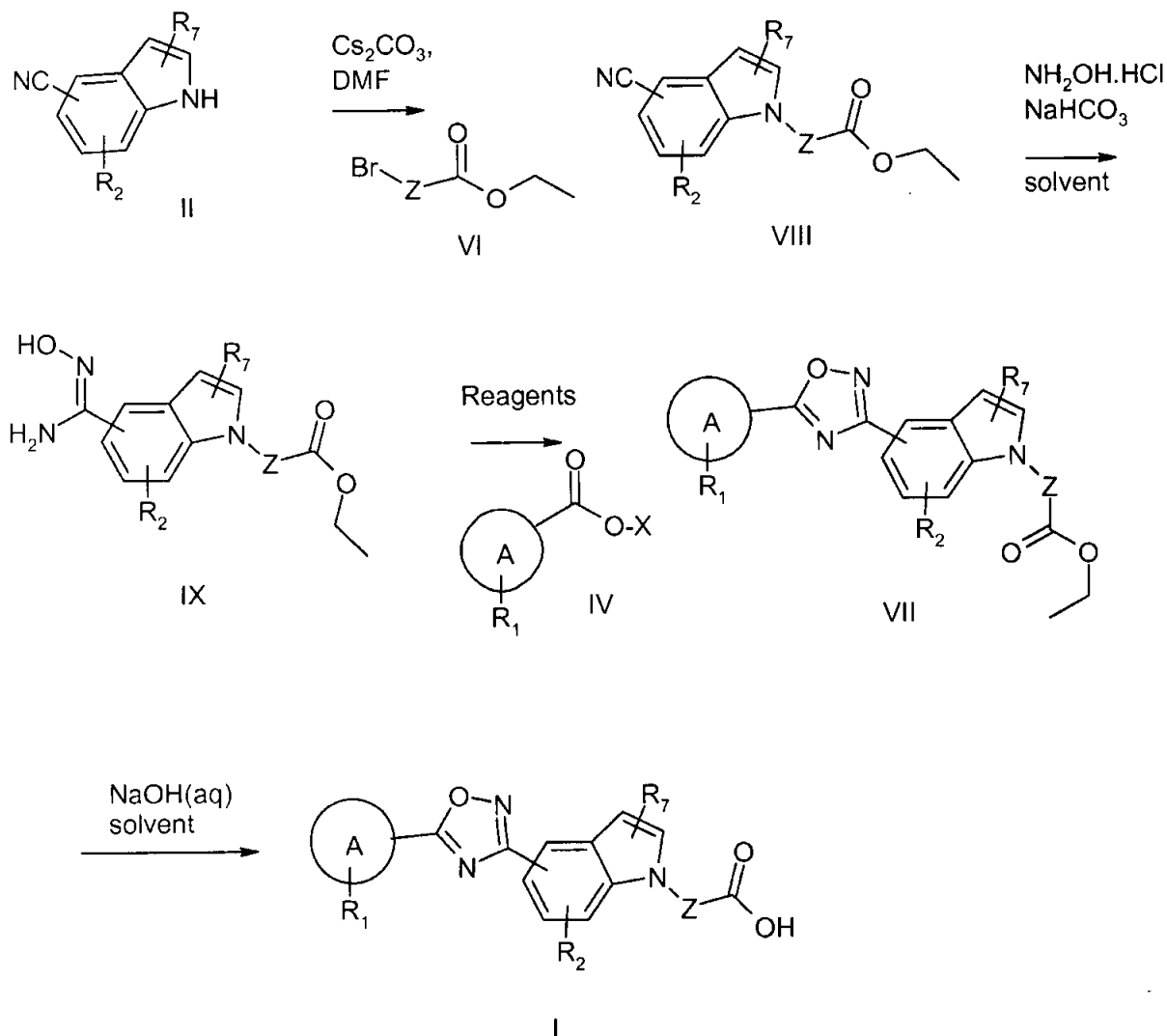
In another aspect the preparation of a compound of formula (I) can be prepared by the process in Scheme II where A, Z, R₁, R₂, R₇ are as defined for formula (I). In the first step the reaction (II to VIII) can be heated to 80 °C. The second step of the process (VIII to IX) is carried out in a suitable solvent such as ethanol or methanol. The third step of this process (IX to VII) requires amide coupling reagents such as EDC.HCl and HOBT in a solvent such as DMF at a temperature between room temperature and 120 °C. The fourth step of the process is carried out in a suitable solvent such as ethanol or methanol. Compounds of formula (IV) are either commercially available, may be prepared by using methods described in the literature or can be prepared as described in the experimental section. Bromides of formula VI are either commercially available or may be prepared by using methods described in the literature or by the methods disclosed.

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Scheme II



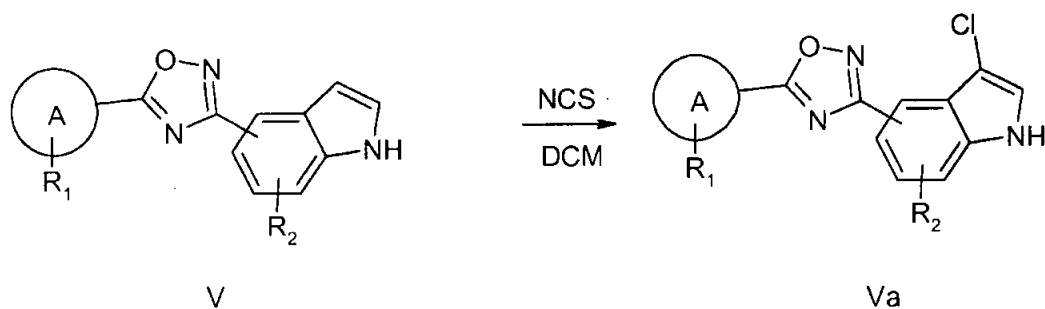
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In cases where the substituent R_7 in formula I is a chlorine atom attached to C-3 of the indole ring this may be introduced in a number of ways. Intermediate (V) in scheme I where $R_7 = \text{H}$ and R_1 , R_2 and A are defined as in formula (I) may be treated with *N*-chlorosuccinimide in dichloromethane to generate the 3-chloro-compound

10 (Va) which can then be converted to (I) as described in scheme I (Scheme III)

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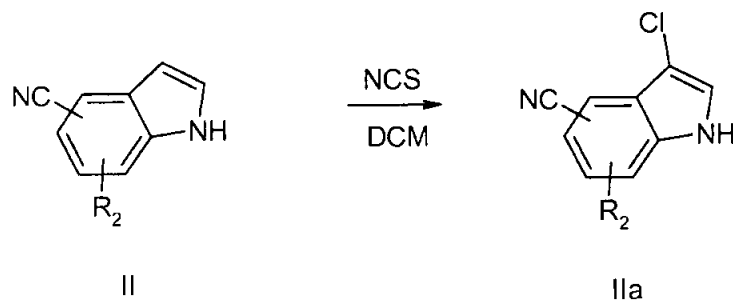
Scheme III



- 5 Alternatively, the intermediate (II) where R₇ = H may be chlorinated by treatment with *N*-chlorosuccinimide in DMF to generate a 3-chloro-indole (IIa) which can be converted to a compound of structure (I) as described in scheme II (Scheme IV).

Scheme IV

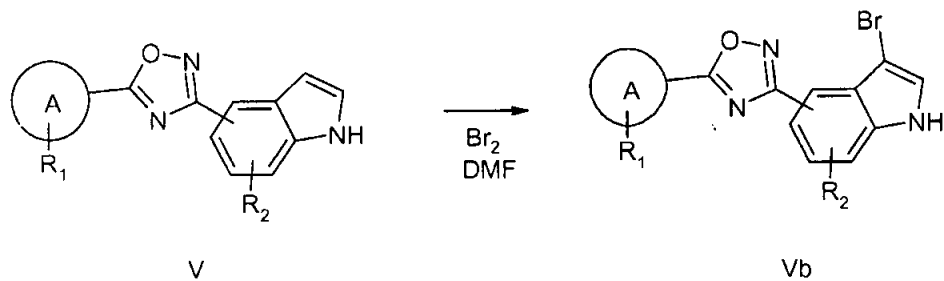
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Where R₇ = Br the intermediate (V) where R₇ = H and A, R₁ and R₂ are as defined in formula (I) may be brominated by treatment with Br₂ in DMF to generate (Vb) where R₇ = Br (Scheme V).

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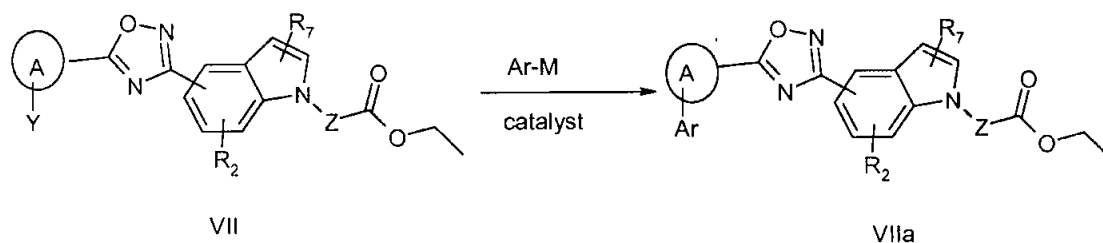
Scheme V



In cases where R_1 is a phenyl group it is possible to introduce this group by a cross-coupling reaction on a compound of structure VII to generate VIIa (Scheme VI) where A, Z, R_2 and R_7 are as defined in formula (I), and Ar is optionally substituted phenyl, followed by hydrolysis to compound I. In this transformation, M is a group such as $B(OH)_2$ which allows the cross-coupling reaction to occur, Y is a group such as bromine, iodine or trifluoromethanesulfonate and the catalyst a palladium species such as tetrakis(triphenylphosphine) palladium(0). Such reactions are typically carried out at elevated temperature.

Scheme VI

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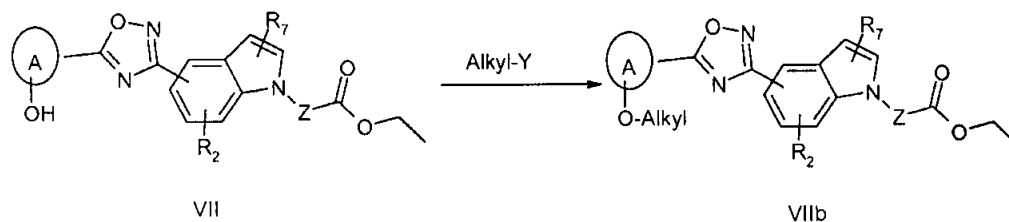


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In cases where R_1 is an alkoxy group such as O-ethyl or O-isopropyl the alkyl substituent can be introduced into a compound of formula VII where $R_1 = OH$ and A, Z, R_7 and R_2 are as defined in formula (I) to generate a compound of formula VIIb where $R_1 = O\text{-alkyl}$ (Scheme VII). In this case Y is a halogen such as iodine. The reaction may be performed in a polar solvent such as DMF in the presence of a base such as potassium carbonate.

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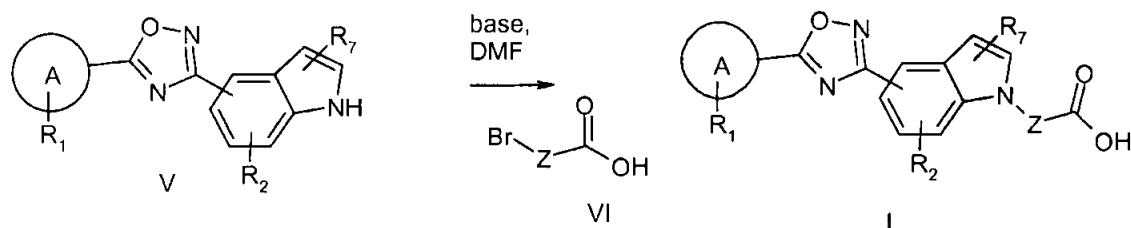
Scheme VII



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In certain cases it is possible to alkylate the intermediate indole (V) where R_1 , R_2 , R_7 and A are as defined in formula (I) directly with carboxylic acid-substituted alkyl bromide to generate the final compound (I) without the need for a hydrolysis step (Scheme VIII). A suitable base for this transformation is cesium carbonate.

Scheme VIII



- 5 Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

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
10 receptor as described herein or by the yeast binding assay, also 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
15 of use in the treatment of conditions or disorders which are mediated via the S1P1
receptor. In particular the compounds of formula (I) and their pharmaceutically
acceptable salts are of use in the treatment of multiple sclerosis, autoimmune
diseases, chronic inflammatory disorders, asthma, inflammatory neuropathies,
arthritis, transplantation, Crohn's disease, ulcerative colitis, lupus erythematosus,
20 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").

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

Thus the invention also provides a compound of formula (I) or a pharmaceutically
acceptable salt thereof, for use as a therapeutic substance, in particular in the
30 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,

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autoimmune diseases, chronic inflammatory disorders, asthma, inflammatory neuropathies, arthritis, transplantation, Crohn's disease, ulcerative colitis, lupus erythematosus, psoriasis, ischemia-reperfusion injury, solid tumours, and tumour metastasis, diseases associated with angiogenesis, vascular diseases, pain
5 conditions, acute viral diseases, inflammatory bowel conditions, insulin and non-insulin dependant diabetes. 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
10 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
15

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
20 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
25 (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
30 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.

35 Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents (e.g. pregelatinised maize

starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); tableting lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); and acceptable wetting agents (e.g. sodium lauryl sulphate). The tablets
5 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
10 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,
15 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
20 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
25 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,
30 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
35 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.

- 5 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
10 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.

- 15 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
20 formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

- For intranasal administration, the compounds of formula (I) or pharmaceutically
25 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
30 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,
35 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

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suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

5 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
10 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. For example, the compounds of the invention may be used in combination with cyclosporin A, methotrexate, steroids, rapamycin,
15 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
20 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 hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, iodine, and chlorine, such as ^3H , ^{11}C , ^{14}C , ^{18}F , ^{123}I and ^{125}I .

25 Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ^3H , ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution
30 assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^{18}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., ^2H ,
35 can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence,

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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.

5

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.

10

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

Conditions, Hardware and Software for Analytical LCMS Systems

Hardware

Agilent 1100 Gradient Pump

Agilent 1100 Autosampler

Agilent 1100 DAD Dectector

Agilent 1100 Degasser

20

Agilent 1100 Oven

Agilent 1100 Controller

Waters Acquity Binary Solvent Manager

Waters Acquity Sample Manager

Waters Acquity PDA

25

Waters ZQ Mass Spectrometer

Sedere Sedex 55, Sedere Sedex 85, Sedere Sedex 75 or Polymer Labs PL-ELS-2100

Software

Waters MassLynx version 4.0 SP2 or version 4.1

30

For 5 minute method

Column

The column used is a Waters Atlantis, the dimensions of which are 4.6mm x 50mm.

The stationary phase particle size is 3 μ m.

35

Solvents

A : Aqueous solvent = Water + 0.05% Formic Acid

B : Organic solvent = Acetonitrile + 0.05% Formic Acid

Method

The generic method used has a 5 minute runtime.

40

Time/min	%B
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0	3
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42

0.1 3
4 97
4.8 97
4.9 3
5 5.0 3

Flow rate

The above method has a flow rate of 3ml/mins

For 2 minute method10 **Software**

Waters MassLynx version 4.1

Column

15

The column used is a Waters Acquity BEH UPLC C18, the dimensions of which are 2.1mm x 50mm. The stationary phase particle size is 1.7 μ m.

Solvents

20

A : Aqueous solvent = Water + 0.05% Formic Acid

B : Organic solvent = Acetonitrile + 0.05% Formic Acid

Weak Wash = 1:1 Methanol : Water

Strong Wash = Water

25

Method

The generic method used has a 2 minute runtime.

Time / min	%B
0	3
0.1	3
1.5	97
1.9	97
2.0	3

30

The above method has a flow rate of 1ml/min.

The injection volume for the generic method is 0.5ul

The column temperature is 40deg

The UV detection range is from 220 to 330nm

35

Open Access Mass Directed Auto Prep System (MDAP)**Hardware**

Open Access Mass Directed Prep instruments consist of the following:

- 1 Waters 600 Gradient pump
- 5 1 Waters 2767 inject / collector
- 1 Waters Reagent manager
- 1 MicroMass ZQ Mass Spectrometer
- 1 Gilson Aspec - waste collector
- 1 Gilson 115 post-fraction UV detector
- 10 1 Computer System.

Software

MicroMass MassLynx v4.0

Column

- The column used is typically a Supelco LCABZ++ column whose dimensions are
- 15 20mm internal diameter by 100mm in length. The stationary phase particle size is 5µm.

Solvents

- A.: Aqueous solvent = Water + 0.1% Formic Acid
- B.: Organic solvent = MeCN: Water 95:5 +0.05% Formic Acid
- 20 Make up solvent = MeOH: Water 80:20 +50mMol Ammonium Acetate
- Needle rinse solvent = MeOH: Water: DMSO 80:10:10

Methods

- One of five methods may be used depending on the analytical retention time of the compound of interest.
- 25 All have a 15-minute runtime, which comprises of a 10-minute gradient followed by a 5-minute column flush and re-equilibration step.
 - MDP 1.5-2.2 = 0-30% B
 - MDP 2.0-2.8 = 5-30% B
 - MDP 2.5-3.0 = 15-55% B
 - 30 MDP 2.8-4.0 = 30-80% B
 - MDP 3.8-5.5 = 50-90% B

Flow Rate

All of the above methods have a flow rate of 20ml/min.

- 35 **Alternative system:.**

Hardware

- Waters 2525 Binary Gradient Module
- 40 • Waters 515 Makeup Pump
- Waters Pump Control Module
- Waters 2767 Inject Collect
- Waters Column Fluidics Manager

44

- Waters 2996 Photodiode Array Detector
- Waters ZQ Mass Spectrometer
- Gilson 202 fraction collector
- Gilson Aspec waste collector

5

Software

Waters MassLynx version 4 SP2

10 Column

The columns used are Waters Atlantis, the dimensions of which are 19mm x 100mm (small scale) and 30mm x 100mm (large scale). The stationary phase particle size is 5m m.

15

Solvents

A : Aqueous solvent = Water + 0.1% Formic Acid

B : Organic solvent = Acetonitrile + 0.1% Formic Acid

20 Make up solvent = Methanol : Water 80:20

Needle rinse solvent = Methanol

Methods

25 There are five methods used depending on the analytical retention time of the compound of interest. They have a 13.5-minute runtime, which comprises of a 10-minute gradient followed by a 3.5 minute column flush and re-equilibration step.

Large/Small Scale 1.0-1.5 = 5-30% B

30

Large/Small Scale 1.5-2.2 = 15-55% B

Large/Small Scale 2.2-2.9 = 30-85% B

35 Large/Small Scale 2.9-3.6 = 50-99% B

Large/Small Scale 3.6-5.0 = 80-99% B (in 6 minutes followed by 7.5 minutes flush and re-equilibration)

40

Flow rate

45

All of the above methods have a flow rate of either 20mls/min (Small Scale) or 40mls/min (Large Scale).

Shallow gradients

5 Large 1.5 to 2.3 min = 13-29% B

Large 1.9 to 2.3 min = 25-41% B

10 Large 2.3 to 2.6 min = 37-53% B

Large 2.6 to 3.1 min = 49-65% B

Large 3.1 to 3.6 min = 61-77% B

15 **Conditions used for NMR**

Hardware

Bruker 400MHz Ultrashield

Bruker B-ACS60 Autosampler

Bruker Advance 400 Console

20 Bruker DPX250

Bruker AVANCE 500

Bruker DRX600

Software

User interface – NMR Kiosk

25 Controlling software – XWin NMR version 3.0

Chromatography

Unless stated otherwise, all chromatography was carried out using silica columns

30

Abbreviations:

g – grams

mg – milligrams

ml – millilitres

35 ul – microlitres

MeCN – acetonitrile

MeOH – methanol

EtOH – ethanol

Et₂O – diethyl ether

40 EtOAc – ethyl acetate

DCM – dichloromethane

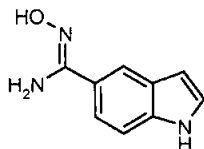
246

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

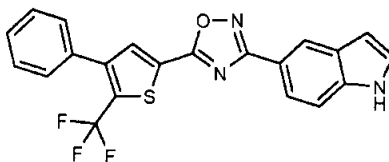
General chemistry section

The intermediates for the preparation of the examples may not necessarily have
35 been prepared from the specific batch described.

47

Description for D1***N*-Hydroxy-1*H*-indole-5-carboximidamide (D1)**

5-Cyanoindole (1.00 g), hydroxylamine.HCl (978 mg) and NaHCO₃ (2.95 g) were dissolved/suspended in MeOH (14 ml), heated to 50 °C and stirred overnight. LCMS analysis showed the reaction was incomplete after this time so a further portion of hydroxylamine.HCl (978 mg) was added and the reaction temperature raised to 80 °C. The reaction was complete after 4 hours. The reaction mixture was cooled to RT and evaporated to dryness under reduced pressure. The residue was treated with 1M aqueous HCl (50 ml) and extracted with EtOAc (2 x 50 ml). This failed to extract the product from the aqueous solution so it was treated with 2M aqueous NaOH to adjust the pH to approximately 7 then re-extracted with EtOAc (3 x 50 ml). The combined organics were washed with brine (30 ml), dried over MgSO₄, filtered and evaporated to dryness to give the title compound (1.36 g) as a brown oil. δ H (MeOD, 400MHz) 6.50 (1H, s), 7.27 (1H, s), 7.36-7.45 (2H, m), 7.88 (1H, s). MS (ES): C₉H₈N₃O requires 175; found 176 (MH⁺).

Description for D2**5-{5-[4-Phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1*H*-indole (D2)**

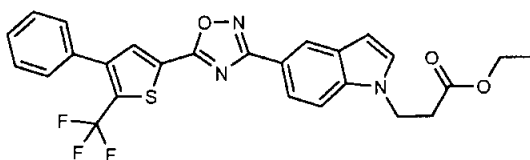
D1 (174 mg) and methyl 4-phenyl-5-(trifluoromethyl)-2-thiophenecarboxylate (286 mg) were combined, treated with sodium ethoxide (21 % wt in EtOH, 411 μ l) and heated to 120 °C in a microwave reactor for 30 minutes. LCMS analysis showed the reaction was incomplete so microwave heating was continued for a further two periods of 30 minutes. The reaction mixture was then cooled to RT, quenched with H₂O (2 ml) and evaporated to dryness under reduced pressure to give the crude product (411 mg) as a brown solid. The crude residue was purified on a 40+S Biotage cartridge, eluting with a 0 to 50 % mixture of Et₂O in petroleum ether. This gave the title compound (122 mg) as an off-white solid. δ H (CDCl₃, 400MHz): 6.68

48

(1H, s), 7.30 (1H, t), 7.41-7.55 (6H, m), 7.92 (1H, s), 7.99 (1H, d), 8.36 (1H, br. s), 8.50 (1H, s). MS (ES): $C_{21}H_{12}F_3N_3OS$ requires 411; found 410 ($M-H^+$).

Description for D3

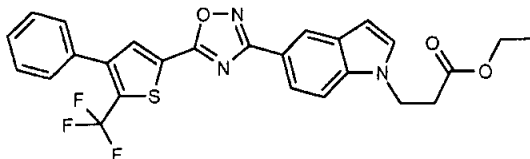
- 5 **Ethyl 3-(5-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate (D3)**



- D2** (100 mg) was dissolved in DMF (1.2 ml), treated with K_2CO_3 (50 mg) then ethyl 3-bromopropionate (90 mg) and heated to 130 °C overnight. After this time LCMS showed the reaction to be incomplete so further ethyl 3-bromopropionate was added (45 mg) and stirring continued at 130 °C for 2 hours. LCMS showed no change so the reaction mixture was evaporated then partitioned between DCM and H_2O . The organic layer was removed and the aqueous solution extracted with DCM. The combined organics were dried over $MgSO_4$, filtered and evaporated to give the crude product (148 mg). This was purified on a silica cartridge (25+S), eluting with a 0 to 25 % mixture of EtOAc in petroleum ether and then again on a 25+M cartridge with a 0 to 30 % mixture of EtOAc in petroleum ether to give the title compound MF105672-144A3 (38 mg) as a white solid. δH ($CDCl_3$, 400MHz): 1.21 (3H, t), 2.85 (2H, t), 4.12 (2H, q), 4.50 (2H, t), 6.60 (1H, d), 7.21 (1H, d), 7.42-7.52 (6H, m), 7.91 (1H, s), 8.00 (1H, d), 8.46 (1H, s). MS (ES^+): $C_{26}H_{20}F_3N_3O_3S$ requires 511; found 512 (MH^+).

Description for D3 (Alternative procedure)

Ethyl 3-(5-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate (D3)

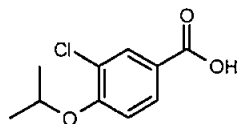


25

5-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1H-indole (**D2**) (600 mg), ethyl 3-bromopropionate (374 μ l), caesium carbonate (950 mg) and DMF were heated at 140 °C for 1 hour in a microwave reactor. A further 1 eq. of ethyl 3-bromopropionate (187 μ l) was added and the mixture heated for 30 minutes. The

reaction mixture was then evaporated, dissolved in DCM and filtered to give the title compound (650 mg) as a brown solid. δ H (CDCl₃, 400MHz): 1.21 (3H, t), 2.85 (2H, t), 4.13 (2H, q), 4.50 (2H, t), 6.61 (1H, d), 7.22 (1H, d), 7.44-7.52 (6H, m), 7.89-7.92 (1H, m), 7.98-8.02 (1H, m), 8.45-8.46 (1H, m). MS (ES): C₂₆H₂₀F₃N₃O₃S requires 511; found 512 (MH⁺).

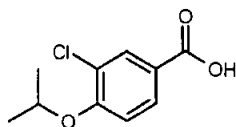
Description for D4 3-Chloro-4-[(1-methylethyl)oxy]benzoic acid (D4)



Propan-2-ol (2.45 ml) and PPh₃ (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 H₂O. This solution was washed with Et₂O, acidified to pH = 1 and extracted with Et₂O. These latter extracts were dried over MgSO₄, filtered and evaporated to give the title compound (4.16 g) as a white solid. δ H (MeOD, 400MHz): 1.37 (6H, d), 4.77 (1H, septet), 7.12 (1H, d), 7.90 (1H, d), 7.98 (1H, s). MS (ES): C₁₀H₁₁ClO₃ requires 214; found 215 (MH⁺).

Alternative synthesis:

3-Chloro-4-[(1-methylethyl)oxy]benzoic acid (D4)

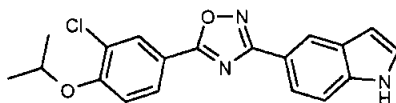


Methyl-4-hydroxy-3-chloro benzoate (13.4 g) was dissolved in DMF (150 ml), treated with K₂CO₃ (19.9 g) followed by isopropyl bromide (13.5 ml) and the resultant mixture heated to 70 °C and stirred overnight. The reaction mixture was then cooled to RT, evaporated to dryness, re-dissolved in EtOH, filtered and evaporated once more to give the intermediate ester (22.2 g) as a white solid. This compound was a mixture of ethyl and methyl esters and used crude in the next reaction.

The crude intermediate (22.2 g) was dissolved in MeOH (75 ml), treated with 2M aqueous NaOH (75 ml), heated to 60 °C and stirred for 2 hours. The reaction mixture was then cooled to RT, the MeOH evaporated and the remaining aqueous solution acidified with 5M aqueous HCl (30 ml). The precipitate was filtered off and dried to give the title compound (15.1 g) as a white solid. δ H (CDCl₃, 400MHz): 1.42 (6H, d), 4.70 (1H, septet), 6.97 (1H, d), 7.97 (1H, d), 8.12 (1H, s). MS (ES): C₁₀H₁₁ClO₃ requires 214; found 213 (M-H⁺).

Description for D5 MF105672-175A2

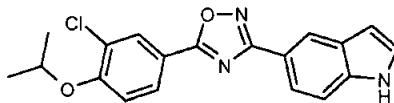
10 **5-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indole (D5)**



D1 (500 mg), **D4** (611 mg) and PyBOP (1.66 g) were dissolved in DMF and stirred overnight. The reaction mixture was then evaporated and partitioned between EtOAc and H₂O. The organic layer was washed with H₂O (x 2) then brine, dried over MgSO₄, filtered and evaporated to give the crude product. This was purified on a silica cartridge, eluting with a 0 to 50 % mixture of Et₂O in hexane to give the title compound (120 mg) as a white solid. δ H (CDCl₃, 400MHz): 1.43 (6H, d), 4.69 (1H, septet), 6.92 (1H, s), 7.04 (1H, d), 7.25 (1H, s), 7.48 (1H, d), 8.00 (1H, d), 8.07 (1H, d), 8.25 (1H, s), 8.39 (1H, br. s), 8.50 (1H, s). MS (ES): C₁₉H₁₆ClN₃O₂ requires 353; found 354 (MH⁺).

Description for D5 (alternative procedure)

25 **5-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indole (D5)**



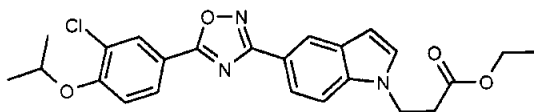
30 A mixture of 5-cyanoindole (5.00 g), NH₂OH.HCl (6.11 g) and NaHCO₃ (14.77 g) in EtOH (176 ml) was heated at 70 °C under an atmosphere of Ar overnight and then at 80 °C for 2.5 hours. The reaction mixture was then filtered and evaporated to give a yellow-orange solid (crude material **D1**).

87

D4 (7.55 g), HOBT (5.23 g) and EDCI (7.42 g) were dissolved in DMF (88 ml). This mixture was stirred for 10 minutes and then the yellow-orange solid from above (6.16 g) dissolved in DMF (88 ml) was added. The reaction mixture was heated to 80 °C overnight then evaporated and partitioned between EtOAc and H₂O. The phases were separated and the aqueous solution extracted with two further portions of EtOAc. The combined organic solutions were dried and evaporated. Part of the crude residue was purified on a 40+M Biotage cartridge, eluting with a 5-30 % mixture of EtOAc in hexane. This gave the title compound (1.45 g) as an off-white solid. δ H (CDCl₃, 400MHz): 1.45 (6H, d), 4.72 (1H, septet), 6.66-6.69 (1H, m), 7.06 (1H, d), 7.29 (1H, apparent triplet or dd), 7.50 (1H, d), 8.01 (1H, dd), 8.08 (1H, dd), 8.27 (1H, d), 8.49-8.52 (1H, m). MS (ES): C₁₉H₁₆ClN₃O₂ requires 353; found 354 (MH⁺). The remaining crude residue was triturated with cold MeOH to give the title compound (3.54 g) as an off white solid. MS data as above.

Description for D6

Ethyl 3-[5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoate (D6)

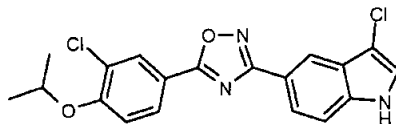


D5 (100 mg) was dissolved in DMF (1.5 ml). To this solution was added K₂CO₃ (58 mg) followed by ethyl 3-bromopropionate (72 μ l) and the mixture stirred and heated to 100 °C. After 1 hour only 5 % conversion was observed by LCMS so further portions of K₂CO₃ (97 mg) and ethyl 3-bromopropionate (72 μ l) were added. After 3 hours the reaction mixture was evaporated then partitioned between DCM and H₂O. The aqueous layer was extracted with DCM then the combined DCM solutions were washed with brine, dried over MgSO₄, filtered and evaporated to give the crude product. This was purified on a silica cartridge, eluting with a 0 to 50 % mixture of Et₂O in petroleum ether. This gave the title compound (40 mg) as a white solid. δ H (CDCl₃, 400MHz): 1.21 (3H, t), 1.45 (6H, d), 2.85 (2H, t), 4.13 (2H, q), 4.51 (2H, t), 4.71 (1H, septet), 6.60 (1H, d), 7.07 (1H, d), 7.21 (1H, d), 7.45 (1H, d), 8.02 (1H, d), 8.08 (1H, d), 8.27 (1H, s), 8.47 (1H, s). MS (ES): C₂₄H₂₄ClN₃O₄ requires 453; found 454 (MH⁺).

Description for D7

SZ

3-Chloro-5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indole (D7)

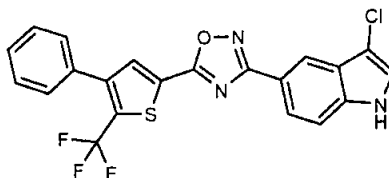


- 5 **D5** (300 mg) and NCS (113 mg) were dissolved in DCM (4.2 ml) and stirred overnight at room temperature. The reaction mixture was then diluted with DCM and washed with H₂O. The aqueous solution was extracted with two further portions of DCM and the combined organic solutions were evaporated to dryness. The crude product was triturated with methanol to give the title compound (42 mg) as a brown solid. The methanol was then evaporated and the resultant brown solid triturated with DCM to give a second batch of the title compound (205 mg) as a brown solid. δ H (d₆-DMSO, 400MHz): 1.37 (6H, d), 4.89 (1H, septet), 7.45 (1H, d), 7.62 (1H, d), 7.70 (1H, s), 7.93 (1H, d), 8.15 (1H, d), 8.24 (1H, s), 8.25 (1H, s), 11.77 (1H, s). MS (ES): C₁₉H₁₅³⁵Cl₂N₃O₂ requires 387; found 388 (MH⁺).

15

Description for D8

3-Chloro-5-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1H-indole (D8)



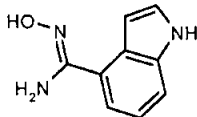
20

- D2** (200 mg) and NCS (65 mg) were dissolved in DCM (5 ml) and stirred overnight at room temperature. The reaction mixture was then partitioned between DCM and H₂O. The DCM solution was evaporated to dryness and purified on a Biotage silica cartridge, eluting with a 25-75 % mixture of diethyl ether in hexane. This gave the title compound (36 mg) as a brown solid. A second batch of the title compound was also obtained from this purification (86 mg) as a brown solid. δ H (CDCl₃, 400MHz): 7.28 (1H, m), 7.45-7.54 (6H, m), 7.93 (1H, s), 8.05 (1H, d), 8.28 (1H, br s), 8.49 (1H, s). MS (ES): C₂₁H₁₁ClF₃N₃OS requires 445; found 444 (M-H⁺).

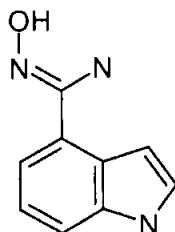
30

Description 9

03

N-Hydroxy-1H-indole-4-carboximidamide (D9)

4-Cyanoindole (850 mg) was dissolved in EtOH (25 ml). To this solution was added NaHCO₃ (2.51 g) and NH₂OH.HCl (831 mg). The mixture was heated to 70 °C and stirred overnight. The reaction was incomplete so was heated at 80 °C for a further 4 hours. The reaction mixture was filtered and evaporated to give the title compound (980 mg) as a yellow semisolid. No purification attempted.

Description for D9 (alternative procedure)**N-Hydroxy-1H-indole-4-carboximidamide (D9)**

15

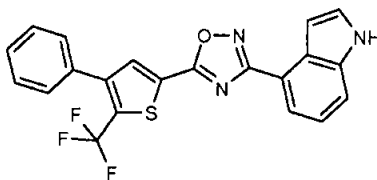
A mixture of 4-cyanoindole (5.0g, 35.2 mmol), sodium hydrogen carbonate (8.9g, 105.6 mmol) and hydroxylamine hydrochloride (4.9g, 70.4 mmol) in ethanol (200ml) was heated at 55 °C overnight. Sodium hydrogen carbonate (5.9g, 70 mmol) and hydroxylamine hydrochloride (4.9g, 70.4 mmol) was added. The mixture was heated for 4 days until only a small amount of starting material was present. The inorganics were filtered off, washing the solid well with ethanol and evaporated off the solvent. The residue was triturated with diethyl ether to give 5.8g of off-white solid. ¹H (400 MHz, methanol-d₄) 6.76-6.78 (1H, m), 7.12 (1H, t), 7.24 (1H, dd), 7.29-7.33 (1H, m) 7.46 (1H, dd).

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Description for D10

4-{5-[4-Phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1H-indole (D10)

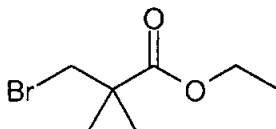
34



4-Phenyl-5-(trifluoromethyl)-2-thiophenecarboxylic acid (310 mg), HOBT (170 mg) and EDCI.HCl (242 mg) were dissolved in DMF (3 ml) and stirred at room temperature for 20 mins. **D9** (200 mg) was dissolved in DMF (3 ml) and added to the
5 above solution and stirring continued at room temperature for two hours. The reaction mixture was then heated to 90 °C, cooled to RT, stood overnight, re-heated to 80 °C and stirred for 3 hours, cooled to room temperature and evaporated to dryness. The residue was re-dissolved in H₂O and extracted with EtOAc (x 3) and the combined organic extracts evaporated to dryness. The residue was purified by
10 flash silica chromatography, eluting with a 25-75 % mixture of diethyl ether in hexane to give the title compound (265 mg) as a brown solid. A sample of this compound (100 mg) was purified by MDAP to give the title compound (62 mg) as an off white solid. δ H (CDCl₃, 400MHz): 7.33-7.36 (2H, m), 7.41-7.42 (1H, m), 7.46-7.52 (5H, m), 7.61 (1H, d), 7.94 (1H, s), 8.06 (1H, d), 8.46 (1H, br s). MS (ES): C₂₁H₁₂F₃N₃OS requires 411; found 412 (MH⁺).
15

Description for D11

Ethyl 3-bromo-2,2-dimethylpropanoate (D11)

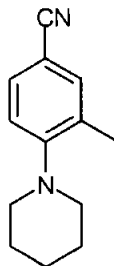


20 3-Bromo-2,2-dimethylpropanoic acid (200 mg) was dissolved in EtOH (5 ml) and treated with concentrated H₂SO₄ (0.4 ml). This mixture was heated at reflux overnight then evaporated. The residue was extracted from H₂O with EtOAc (x 2) and the combined organic solutions dried and evaporated to give the title compound (316 mg) as a clear oil. δ H (CDCl₃, 400MHz) 1.20 (3H, t), 1.32 (6H, s), 3.51 (2H, s), 4.18
25 (2H, q).

Description for D12

3-Ethyl-4-(1-piperidiny)benzonitrile (D12)

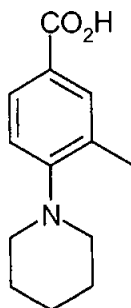
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4-Amino-3-ethylbenzonitrile (3.0 g, 20.5 mmol), 1,5-dibromopentane (11.1 mL, 82.1 mmol), potassium carbonate (5.67 g, 41.0 mmol) and water (39.6 mL) were all split equally between ten microwave vials and each heated at 160 °C for 1 h. All reaction
5 mixtures were combined and extracted twice with ethyl acetate (40 mL) and the combined organic fractions dried (phase separator) and concentrated *in vacuo*. Dichloromethane was added and then the mixture filtered before the filtrate was purified by silica chromatography, eluting 2-5 % ethyl acetate in hexane to give the
10 title compound as a colourless oil (823 mg, 3.85 mmol). Analysis indicated that the compound contained a small dibromopentane impurity. δ H (methanol- d_4 , 400 MHz) 7.52 (1H, dd), 7.47 (1H, dd), 7.13 (1H, d), 2.89 (4H, dd), 2.71 (2H, q), 1.76-1.71 (4H, m), 1.64-1.56 (2H, m), 1.25 (3H, t). MS (ES): $C_{14}H_{18}N_2$ requires 214; found 215 (MH^+).

15 **Description for D13**

3-Ethyl-4-(1-piperidinyl)benzoic acid (D13)



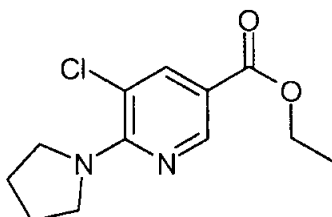
3-ethyl-4-(1-piperidinyl)benzonitrile (**D12**) (817 mg, 3.82 mmol) and potassium hydroxide (2.14 g, 38.2 mmol) in ethanol (35 mL) and water (8 mL) were heated to
20 90 °C (block temperature) for 9 h. Further potassium hydroxide (2.14 g, 38.2 mmol) and water (8 mL) were added and the reaction heated for a further 18 h. The reaction was allowed to cool and was neutralised with aqueous HCl. A white solid was collected by filtration and an attempt was made to purify the filtrate by SCX cartridge, but this failed. Both the solid and product of SCX were combined,

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methanol added and then the mixture acidified with acetic acid. The mixture was filtered to obtain the filtrate, which was then trapped on SCX cartridge, washed with methanol and eluted with 2M ammonia in methanol. On test scale this gave the title compound as a white solid (96 mg, 0.41 mmol) and on the remaining material gave a colourless oil (563 mg, 2.41 mmol). δ H (methanol- d_4 , 400 MHz): 7.85 (1H, d), 7.74 (1H, dd), 7.03 (1H, d), 2.85 (4H, dd), 2.73 (2H, q), 1.72 (4H, m), 1.61 (2H, m), 1.25 (3H, t) ppm. MS (ES): $C_{14}H_{19}NO_2$ requires 233; found 234 (MH^+).

Description for D14

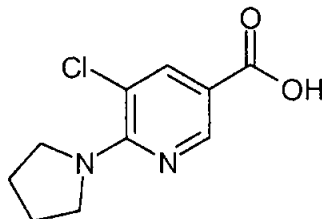
10 Ethyl 5-chloro-6-(1-pyrrolidinyl)-3-pyridinecarboxylate (D14)



A mixture of 5,6-dichloronicotinic acid ethyl ester (1.00 g, 4.57 mmol), pyrrolidine (325 mg, 4.57 mmol), potassium carbonate (632 mg, 4.57 mmol) and copper powder (34 mg) in DMF (6.8 mL) was heated at 130 °C in the microwave for 20 min. Further pyrrolidine (163 mg, 2.29 mmol) was added and the reaction heated at 130 °C for 20 min. Water (7 mL) was added and the mixture extracted with ethyl acetate (2 x 14 mL). The combined organic extracts were washed with water (7 mL) and brine (7mL) before being dried (phase separator) and concentrated *in vacuo* to give the title compound as an orange oil (1.06 g, 4.17 mmol). δ H (methanol- d_4 , 400 MHz): 8.45 (1H, d), 7.98 (1H, d), 4.31 (2H, q), 3.82-3.75 (4H, m), 2.0-1.93 (4H, m), 1.36 (3H, t) ppm. MS (ES): $C_{12}H_{15}ClN_2O_2$ requires 254, 256; found 255, 257 (MH^+).

25 Description for D15

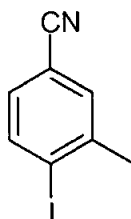
5-Chloro-6-(1-pyrrolidinyl)-3-pyridinecarboxylic acid (D15)



SA

Ethyl 5-chloro-6-(1-pyrrolidinyl)-3-pyridinecarboxylate (**D14**) (1.06 g, 4.16 mmol) in ethanol (20 mL) and aqueous sodium hydroxide (2M, 2.08 mL, 4.16 mmol) was heated at 40 °C for 18 h. The reaction mixture was allowed to cool and was neutralised with 2M HCl (aq.). The title compound formed as a white solid and was filtered off and washed with methanol to give the title compound (243 mg, 1.08 mmol) SJ108923-113A3. The filtrate was trapped on an SCX column, eluting with 2M ammonia in methanol to give further title compound as an orange solid (467 mg, 2.07 mmol). δ H (methanol- d_4 , 400 MHz): 8.55 (1H, d), 8.03 (1H, d), 3.76-3.70 (4H, m), 1.96-1.90 (4H, m). MS (ES): $C_{10}H_{11}ClN_2O_2$ requires 226, 228; found 227, 229 (MH^+).

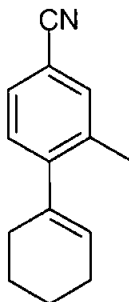
10

Description for D16**3-Ethyl-4-iodobenzonitrile (D16)**

To 4-amino-3-ethylbenzonitrile (2.50 g, 17.1 mmol) stirred in water (14 mL) at 0 °C was added concentrated hydrochloric acid (7.80 mL, 257 mmol) dropwise followed by a solution of sodium nitrite (1.24 g, 18.0 mmol) in water (3.43 mL) dropwise. The resultant mixture was stirred for 15 minutes and then added over 15 minutes to a solution of potassium iodide (2.98 g, 18.0 mmol) in water (6.0 mL) at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was extracted with ethyl acetate (3 x 100 mL) and the combined organic fractions washed with brine (100 mL), dried (phase separator) and concentrated *in vacuo* to give the title compound as a brown solid (4.21 g, 16.4 mmol). δ H (methanol- d_4 , 400 MHz): 8.02 (1H, d), 7.61 (1H, d), 7.24 (1H, dd), 2.80 (2H, q), 1.21 (3H, t). MS (ES): No mass ion observed.

25

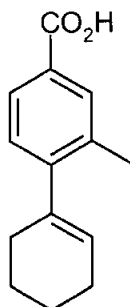
Description for D17**4-(1-Cyclohexen-1-yl)-3-ethylbenzonitrile (D17)**



A mixture of 3-ethyl-4-iodobenzonitrile (**D16**) (1.23 g, 4.80 mmol), 1-cyclohexen-1-ylboronic acid (907 mg, 7.20 mmol), sodium methoxide (778 mg, 14.4 mmol) and bis(triphenylphosphine)palladium (II) chloride (337 mg, 0.48 mmol) in anhydrous methanol (12 mL) was heated at 80 °C for 10 minutes in the microwave. The reaction mixture was partitioned between ethyl acetate (40 mL) and water (40 mL) before the organic layer was further washed with water (40 mL), dried (phase separator) and concentrated *in vacuo*. The crude material was purified by silica chromatography, eluting 0-5 % EtOAc in hexane over 30 minutes to give the title compound as a yellow oil (824 mg, 3.91 mmol). δ H (methanol- d_4 , 400 MHz) 7.56 (1H, d), 7.46 (1H, dd), 7.19 (1H, d), 5.61-5.56 (1H, m), 2.68 (2H, quart), 2.23-2.16 (4H, m), 1.85-1.68 (4H, m), 1.20 (3H, t). MS (ES): No mass ion observed.

Description for D18

15 **4-(1-Cyclohexen-1-yl)-3-ethylbenzoic acid (D18)**



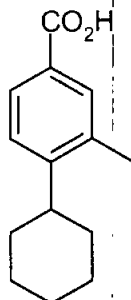
4-(1-cyclohexen-1-yl)-3-ethylbenzonitrile (**D17**) (824 mg, 3.91 mmol) and potassium hydroxide (2.19 g, 39.1 mmol) in ethanol (36 mL) and water (8 mL) were heated at 90 °C (block temperature) for 20 h. The reaction mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate (120 mL) and aqueous hydrochloric acid (2M, 50 mL) before the organic phase was washed with further hydrochloric acid (2M, 50 mL), dried (phase separator) and concentrated *in vacuo* to give the title compound as a yellow oil (808 mg, 3.51 mmol). δ H (methanol- d_4 , 400

59

MHz) 7.87 (1H d), 7.76 (1H dd), 7.11 (1H, d) 5.59-5.54 (1H, m), 2.68 (2H, q), 2.25-2.15 (4H, m), 1.84-1.67 (4H, m), 1.20 (3H, t). LCMS (ES): $C_{15}H_{18}O_2$ requires 230; found 229 ($M-H^+$).

5 **Description for D19**

4-Cyclohexyl-3-ethylbenzoic acid (D19)

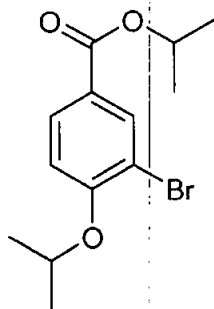


10 4-(1-cyclohexen-1-yl)-3-ethylbenzoic acid (**D18**) (803 mg, 3.49 mmol) was dissolved in methanol (70 mL) and hydrogenated on an H-Cube using a palladium on carbon cartridge. The product solution was concentrated *in vacuo* to give the title compound as a white solid (792 mg, 3.41 mmol). δ H (methanol- d_4 , 400 MHz): 7.82-7.68 (2H, m), 7.33 (1H, d), 2.83 (1H, m), 2.73 (2H, q), 1.87 (2H, m), 1.85-1.70 (3H, m), 1.58-1.30 (5H, m), 1.22 (3H, t). LCMS (ES): no mass ion observed.

15

Description for D20

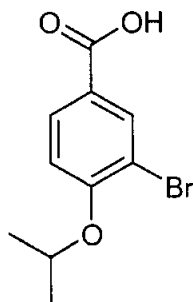
1-Methylethyl 3-bromo-4-[(1-methylethyl)oxy]benzoate (D20)



20 A mixture of 3-bromo-4-hydroxybenzoic acid (2.00 g, 9.22 mmol), 2-iodopropane (1.85 mL, 18.4 mmol) and potassium carbonate (2.55 g, 18.4 mmol) in DMF (175 mL) was heated to reflux for 5 h. The reaction was allowed to cool and was filtered. The filtrate was concentrated *in vacuo* and the residue partitioned between ethyl acetate (150 mL) and water (150 mL), which was basified with 2M NaOH. The

organic phase was dried (phase separator) and concentrated *in vacuo* to give the title compound as a yellow oil (2.36 g, 7.84 mmol). δ H (methanol- d_4 , 400 MHz): 8.05 (1H, d), 7.90 (1H, dd), 7.25 (1H, d), 5.10 (1H, septet), 4.81 (1H, septet), 1.32 (6H, d), 1.31 (6H, d) ppm. MS (ES): no mass ion observed.

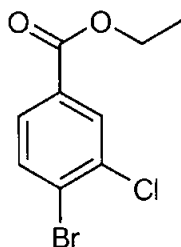
5

Description for D21**3-Bromo-4-[(1-methylethyl)oxy]benzoic acid (D21)**

10

A solution of 1-methylethyl 3-bromo-4-[(1-methylethyl)oxy]benzoate (**D20**) (2.36 g, 7.84 mmol) in ethanol (100 mL) and aqueous sodium hydroxide (2M, 39 mL) was heated to reflux for 5 h. The reaction mixture was concentrated *in vacuo* and partitioned between ethyl acetate (125 mL) and water (125 mL), the latter acidified with 2M HCl (40 mL). The aqueous layer was extracted with further ethyl acetate (70 mL) and the combined organic extracts dried (phase separator) and concentrated *in vacuo* to give the title compound as an off-white solid (1.83 g, 7.06 mmol). δ H (methanol- d_4 , 400 MHz): 8.05 (1H, d), 7.89 (1H, dd), 7.23 (1H, d), 4.79 (1H, septet), 1.32 (6H, d). MS (ES): $C_{10}H_{11}BrO_3$ requires 258, 260; found 257, 259 ($M-H^+$).

20

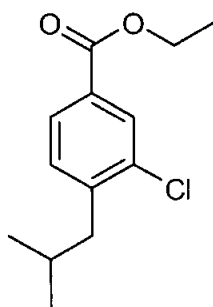
Description for D22**Ethyl 4-bromo-3-chlorobenzoate (D22)**

25

To a suspension of 4-bromo-3-chlorobenzoic acid (5.00 g, 21.2 mmol) in ethanol (50 mL) was added sulphuric acid (5 mL) and the resultant mixture heated to reflux for 60 h. The reaction was partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer was extracted with further ethyl acetate and the combined organic fractions dried (phase separator) and concentrated *in vacuo* to give the title compound as a brown oil/solid (5.09 g, 19.3 mmol). δ H (d_6 -DMSO, 400 MHz): 8.06 (1H, d), 7.96 (1H, d), 7.80 (1H, dd), 4.33 (2H, q), 1.33 (3H, t). MS (ES): no mass ion observed.

10 **Description for D23**

Ethyl 3-chloro-4-(2-methylpropyl)benzoate (D23)

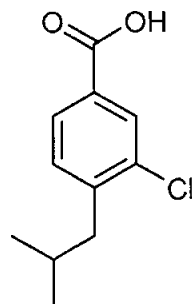


A solution of isobutylzinc bromide in THF (0.5 M, 30 mL, 15.0 mmol) was added under argon to ethyl 4-bromo-3-chlorobenzoate (**D22**) (2.00 g, 7.60 mmol) and then 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (930 mg, 1.14 mmol) was added. The reaction was heated to reflux for 4.5 h. The mixture concentrated *in vacuo* and the residue partitioned between ethyl acetate (125 mL) and water (125 mL). A solid formed, which was filtered off and discarded. The organic layer was washed with water (100 mL), dried (phase separator) and concentrated *in vacuo*. The crude product was purified by silica chromatography, eluting with 0-5 % EtOAc in hexane over 30 minutes to give the title compound as a colourless oil (1.76 g, 7.33 mmol). δ H (d_6 -DMSO, 400 MHz): 7.91 (1H, d), 7.80 (1H, dd), 7.46 (1H, d), 4.30 (2H, q), 2.66 (2H, d), 1.88-2.01 (1H, m), 1.32 (3H, t), 0.89 (6H, d). MS (ES): no mass ion observed.

25

Description for D24

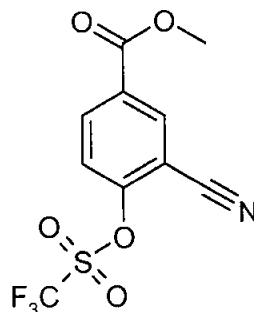
3-Chloro-4-(2-methylpropyl)benzoic acid (D24)



A solution of ethyl 3-chloro-4-(2-methylpropyl)benzoate (**D23**) (1.76 g, 7.33 mmol), and aqueous sodium hydroxide (2M, 3.70 mL, 7.4 mmol) in ethanol (30 mL) was heated at 40 °C for 3 h. The reaction mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate (100 mL) and water (100 mL), the latter acidified with 2M HCl (4 mL). The aqueous layer was extracted with ethyl acetate (100 mL) and the combined organic extracts dried (phase separator) and concentrated *in vacuo* to give the title compound as a white solid (1.35 g, 6.36 mmol). δ H (d_6 -DMSO, 400 MHz): 13.20 (1H, br. s), 7.89 (1H, d), 7.82 (1H, dd), 7.44 (1H, d), 2.64 (2H, d), 1.94 (1H, m), 0.89 (6H, d). MS (ES): $C_{11}H_{13}^{35}ClO_2$ requires 212; found 211 ($M-H^+$).

Description for D25

Methyl 3-cyano-4-[[[(trifluoromethyl)sulfonyl]oxy]benzoate (**D25**)

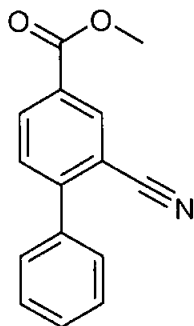


To a solution of methyl 3-cyano-4-hydroxybenzoate (3 g, 16.93 mmol) and triethylamine (3.54 mL, 25.4 mmol) in dry dichloromethane (60 mL) at 0 °C under a flush of argon was added trifluoromethanesulfonic anhydride (3.15 mL, 18.63 mmol) slowly dropwise. The reaction was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was washed with 10 % aqueous potassium carbonate (2 x 50 mL) and then aqueous HCl (2M, 2 x 50 mL) before the organic phase was

dried (phase separator) and the solvent removed *in vacuo* to give the title compound as a dark brown oil, (5.165 g, 16.70 mmol). δ H (CDCl₃, 400 MHz): 8.44 (1H, d), 8.38 (1H, dd), 7.60 (1H, d), 3.99 (3H, s). MS (ES): no mass ion observed.

5 **Description for D26**

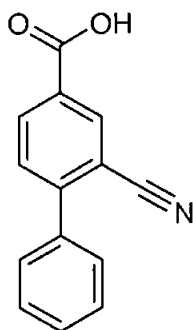
Methyl 2-cyano-4-biphenylcarboxylate (D26)



The following reaction was split into two batches with half the amounts: methyl 3-cyano-4-[[[(trifluoromethyl)sulfonyl]oxy]benzoate (**D25**) (1.5 g, 4.85 mmol),
10 phenylboronic acid (1.183 g, 9.70 mmol), potassium carbonate (2.011 g, 14.55 mmol) and palladium tetrakis(triphenylphosphine)(0) (0.561 g, 0.485 mmol) were taken up in DMF (24 ml) and the mixture heated in the microwave for 30 min at 150 °C. The two reactions were combined and diluted with ethyl acetate (50 mL) and the mixture filtered through kieselguhr to remove palladium residues. The filtrate was
15 concentrated *in vacuo* to reduce the amount of DMF and then the residue partitioned between saturated aqueous sodium bicarbonate (50 mL) and ethyl acetate (50 mL). The organic phase was washed with further sodium bicarbonate (50 mL) and then water (50 mL) before it was dried (MgSO₄), filtered and the solvent removed *in vacuo*. The brown solid was purified by silica chromatography, eluting 0-25 % EtOAc
20 in iso-hexane over 35 minutes to give the title compound as a white solid (935 mg, 3.94 mmol). δ H (d₆-DMSO, 400 MHz): 8.42 (1H, d), 8.29 (1H, dd), 7.81 (1H, d), 7.65 (2H, m), 7.60 -7.50 (3H, m), 3.92 (3H, s). MS (ES): no mass ion observed.

Description for D27

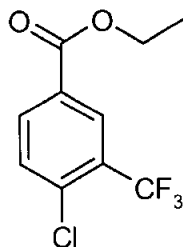
25 **2-Cyano-4-biphenylcarboxylic acid (D27)**



- To methyl 2-cyano-4-biphenylcarboxylate (**D26**) (935 mg, 3.94 mmol) was added ethanol (18 ml) but dissolution did not occur so dichloromethane (10 ml) was added. Sodium hydroxide (2 ml, 4.00 mmol) was then added and the reaction stirred for 2 h.
- 5 To the mixture was added dichloromethane (20 mL) and 2M aqueous HCl (10 mL). The layers were separated and the aqueous extracted with further dichloromethane (20 mL). The combined organic phase was dried (phase separator) and the solvent removed *in vacuo* to give a white solid, which was dissolved in methanol (30 mL) and aqueous sodium hydroxide was added (2M, 3 mL). The reaction was stirred at room
- 10 temperature for 1 h before addition of water (20 mL). The reaction was stirred for a further 1h. Dichloromethane (60 mL) was added and the mixture shaken and the layers separated. The aqueous phase was extracted with further dichloromethane (50 mL) before the combined organic phase was dried (phase separator) and the solvent removed *in vacuo* to give the title compound as a white solid, (849 mg, 3.80
- 15 mmol). δ H (d_6 -DMSO, 400 MHz): 13.60 (1H, br s), 8.38 (1H, d), 8.28 (1H, dd), 7.78 (1H, d), 7.63 (2H, m), 7.60-7.50 (3H, m). MS (ES): $C_{14}H_9NO_2$ requires 223; found 222 ($M-H^+$).

Description for D28

- 20 **Ethyl 4-chloro-3-(trifluoromethyl)benzoate (D28)**



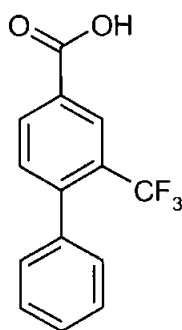
4-Chloro-3-(trifluoromethyl)benzoic acid (1 g, 4.45 mmol) was dissolved in ethanol (3 ml) and concentrated sulfuric acid (0.15 ml) was added. The mixture was heated in

65

the microwave at 100 °C for 5 minutes and then 120 °C for 15 minutes. The solvent was removed in vacuo and the residue partitioned between saturated aq. sodium bicarbonate (50 ml) and ethyl acetate (50 ml). The aqueous layer was extracted with further EtOAc (50 ml) and the organic phases were combined, dried with a phase separator and concentrated in vacuo to give the title compound (1.026 g) (DN108121-148A3) as a colourless oil. δ H (methanol- d_4 , 400 MHz) 1.40 (3H, t), 4.41 (2H, q), 7.76 (1H, d), 8.21 (1H, dd), 8.33 (1H, d). MS (ES) no mass ion observed.

Description for D29

10 **2-(Trifluoromethyl)-4-biphenylcarboxylic acid (D29)**

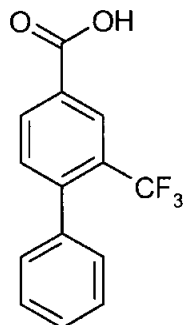


The reaction was split into 4, using a quarter of the reagents in each: to a mixture of 4-bromo-3-(trifluoromethyl)benzonitrile (4 g, 16.00 mmol), phenylboronic acid (3.90 g, 32.0 mmol) and potassium carbonate (6.63 g, 48.0 mmol) in N,N-dimethylformamide (DMF) (64 ml) was added palladium tetrakis(triphenylphosphine)(0) (1.849 g, 1.600 mmol). Each reaction was heated in the microwave at 150 °C for 30 min. The combined reaction mixtures were filtered through celite, washed with ethyl acetate and the solvent removed in vacuo. The residue was partitioned between ethyl acetate (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 dichloromethane 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 h. The reaction mixture was concentrated in vacuo and the residue partitioned between dichloromethane (100 mL) and 2M HCl (100 mL). The organic phase was isolated and dried (phase separator) and the solvent removed in vacuo to give the crude product. Purification using the Biotage Horizon, reverse phase cartridge, eluting 5-

100 % MeCN in water to give an off-white solid the title compound (960 mg) (N2123-46-A5). MS (ES): $C_{14}H_9F_3O_2$ requires 266; found 265 ($M-H^+$).

Description for D29 (Alternative procedure)

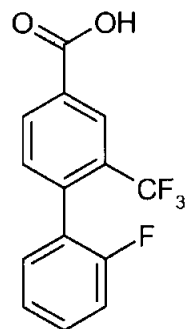
5 **2-(Trifluoromethyl)-4-biphenylcarboxylic acid (D29)**



- Batch A: A mixture of **D98** (1.0 g, 3.96 mmol), phenyl boronic acid (724 mg, 5.94 mmol), palladium acetate (44 mg), (dicyclohexylphosphino)biphenyl (140.2 mg) and potassium fluoride (689 mg, 11.9 mmol) in THF (8 ml) was heated in the microwave at 120 °C for a total of 40 minutes.
- 10 Batch B: A mixture of **D28** (500 mg, 1.98 mmol), phenyl boronic acid (290 mg, 2.38 mmol), palladium acetate (2.2 mg), (dicyclohexylphosphino)biphenyl (7 mg) and potassium fluoride (344 mg, 5.8 mmol) in THF (4 ml) was heated in the microwave at 120 °C for 20 minutes.
- 15 The reaction mixtures from batches A & B were combined, filtered and the filtrate concentrated in vacuo. The residue was purified by flash chromatography (0 to 5% EtOAc in hexane to give a mixture of starting material and coupled product. This material was dissolved in ethanol (10 ml) and 2M NaOH (aq) (5ml) and then heated to reflux for 3 h. The solvent was removed in vacuo and the residue partitioned
- 20 between DCM and 2M aq. HCl. The aq. was extracted with further DCM. The organic phases were combined and concentrated in vacuo. The crude material was purified by reversed phase chromatography on the Horizon eluting with 5 to 100% MeCN in water to afford the title compound as a white solid (367 mg). δH (d_6 -DMSO, 400 MHz) 7.31-7.40 (2H, m), 7.44-7.52 (3H, m), 7.57 (1H, d), 8.24 (1H, dd), 8.29 (1H, d),
- 25 13.57 (1H, br. s). MS (ES): $C_{14}H_9F_3O_2$ requires 266; found 265 ($M-H^+$).

Description for D30

2'-Fluoro-2-(trifluoromethyl)-4-biphenylcarboxylic acid (D30)

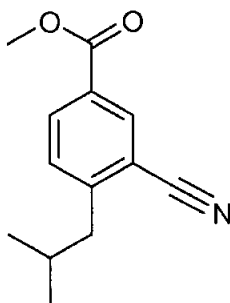


This material was prepared using a similar method to that described for **D29** using (2-fluorophenyl)boronic acid and **D98** except that only a single coupling reaction was performed, similar to batch A and the coupling reaction was heated for 20 minutes.

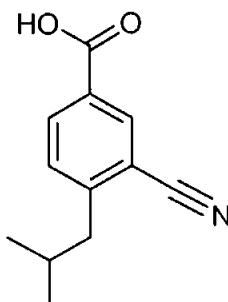
- 5 MS (ES): $C_{14}H_8F_4O_2$ requires 284; found 283 ($M-H^+$).

Description for D31

Methyl 3-cyano-4-(2-methylpropyl)benzoate (D31)



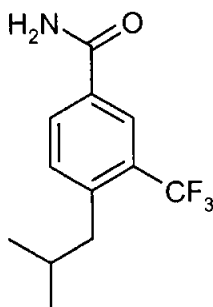
- 10 To methyl 3-cyano-4-[[trifluoromethyl)sulfonyl]oxy]benzoate (**D25**) (1.5 g, 4.85 mmol) was added bromo(2-methylpropyl)zinc (48.5 ml, 24.25 mmol) in tetrahydrofuran (50 ml) under argon. To the solution was then added 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (0.355 g, 0.485 mmol) and the reaction heated to reflux for 6 h. The mixture was
- 15 quenched with water (2 mL) and then filtered through celite, washing with ethyl acetate. The solvent was removed *in vacuo*. The residue was partitioned between ethyl acetate (50 mL) and water (50 mL) and the organic phase dried (phase separator) and the solvent removed *in vacuo*. The residue was purified by silica chromatography, eluting 0-15 % EtOAc in iso-hexane over 40 min. Two batches
- 20 were collected, one of which was the title compound as a colourless oil (233 mg, 1.072 mmol). δH ($CDCl_3$, 400 MHz): 8.28 (1H, d), 8.15 (1H, dd), 7.38 (1H, d), 3.94, 3H, s), 2.78 (2H, d), 2.02 (1H, m), 0.96 (6H, d).

**Description for D32****3-Cyano-4-(2-methylpropyl)benzoic acid (D32)**

- 5 Methyl 3-cyano-4-(2-methylpropyl)benzoate (**D31**) (233 mg, 1.072 mmol) was dissolved in ethanol (4 ml) and 2M aqueous sodium hydroxide (1 ml, 2 mmol) was added. The reaction was stirred for 1 h. 2M aqueous HCl (10 mL) was added and the mixture extracted with dichloromethane (20 mL + 10 mL). The organic phases were isolated and dried by phase separator and combined before the solvent was removed *in vacuo* to give the title compound as a white solid (203 mg, 0.999 mmol).
- 10 δ H (d_6 -DMSO, 400 MHz) 13.43 (1H, br. s), 8.29 (1H, d), 8.14 (1H, dd), 7.59 (1H, d), 2.74 (2H, d), 1.96 (1H, m), 0.91 (6H, d). MS (ES): $C_{12}H_{13}NO_2$ requires 203; found 202 ($M-H^+$).

Description for D33

- 15 **4-(2-Methylpropyl)-3-(trifluoromethyl)benzamide (D33)**

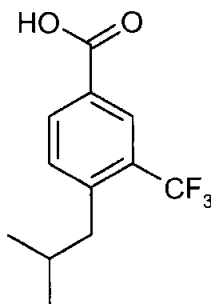


- To a solution of 4-bromo-3-trifluoromethylbenzonitrile (1.25 g, 5.0 mmol) and isobutylzinc bromide (25 mmol) in THF (50 mL, 25 mmol) under argon was added 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex
- 20 (612 mg, 0.75 mmol) and the reaction heated at reflux for 5 h. The mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate (80 mL) and water (80 mL). A solid formed and was filtered off and discarded. The organic layer was washed with water (80 mL) before it was dried (phase separator) and

concentrated *in vacuo* to give the crude title compound as a black oil. This was used directly in the next step (1.35 g).

Description for D34

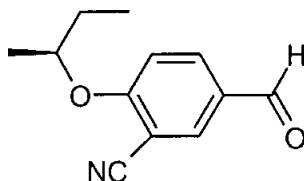
5 **4-(2-Methylpropyl)-3-(trifluoromethyl)benzoic acid (D34)**



4-(2-methylpropyl)-3-(trifluoromethyl)benzamide (**D33**) (1.35 g, 5.50 mmol) was dissolved along with potassium hydroxide (3.09 g, 55.0 mmol) in ethanol (40 ml) and water (10.0 ml) and the solution heated to reflux for 18 h. The reaction mixture was concentrated *in vacuo* and the mixture separated between EtOAc (150 mL) and aqueous sodium hydroxide (2M, 150 mL). The layers were separated and the organic phase extracted with further sodium hydroxide solution (200 mL). LCMS of both phases showed product in both. Therefore the aqueous phase was acidified to pH1 with HCl (5M) and extracted back into EtOAc (2 x 150 mL) and these organic phases combined with the original organic phase. The solvent was removed *in vacuo* and the residue purified by reverse phase chromatography, eluting 5-100 % MeCN in H₂O over 2000 mL and the solvent removed *in vacuo* to give a brown solid (690 mg, 2.410 mmol). This solid was triturated with hexane to give the title compound as a buff solid (135 mg, 0.548 mmol) and the filtrate purified by MDAP to give further title compound as a white solid (102 mg, 0.414 mmol). δ H (d_6 -DMSO, 400 MHz): 13.39 (1H, br. s), 8.16 (1H, s), 8.13 (1H, d), 7.62 (1H, d), 2.69 (2H, d), 1.97 (1H, m), 0.90 (6H, d). MS (ES): C₁₂H₁₃F₃O₂ requires 246; found 245 (M-H⁺).

Description for D35

25 **5-Formyl-2-[[[(1S)-1-methylpropyl]oxy]benzonitrile (D35)**

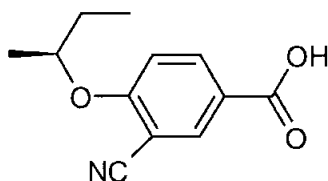


70

(2S)-2-Butanol (0.99 g, 0.013 mol) was dissolved in DMF (50 ml) and the solution cooled to 0 °C. To this was added sodium hydride, (60% dispersion in mineral oil, 1.54g, 0.036 mol) in a portion-wise manner, the mixture was stirred at 0 °C for 10 minutes after complete addition. 2-Fluoro-5-formylbenzonitrile (2.0 g, 0.013 mol) was then added and the reaction mixture allowed to warm to room temperature (slowly within the ice bath) and the reaction mixture was stirred overnight at room temperature. The reaction mixture was then cooled to 0 °C, quenched with brine and diluted with EtOAc (~25ml). The mixture was partitioned and the organic fraction extracted with water (~30ml), the combined organics were dried by passing through a phase separating cartridge and then evaporated to dryness under reduced pressure to give the crude product. The crude residue was purified on a 40+M Biotage cartridge, eluting with a 20 to 50 % mixture of EtOAc in hexane. This gave the title compound (220mg) as a white solid. δ H (d_6 -DMSO, 400 MHz): 9.88 (1H, s), 8.30 (1H, s), 8.15 (1H, d), 7.49 (1H, d), 4.73-4.81 (1H, m), 1.63-1.79 (2H, m), 1.33 (3H, d), 0.95 (3H, t). MS (ES): $C_{12}H_{13}NO_2$ requires 203; found 204 (MH^+).

Description for D36

3-Cyano-4-[[[(1S)-1-methylpropyl]oxy]benzoic acid (D36)

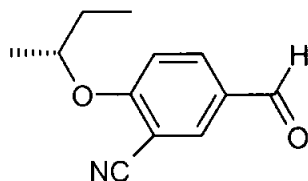


To a solution of 5-formyl-2-[[[(1S)-1-methylpropyl]oxy]benzonitrile (**D35**) (220mg, 1.08 mmol) in acetic acid (20ml) was added sodium perborate tetrahydrate (334mg, 2.17 mmol), the reaction mixture was heated at 50 °C over the weekend. The reaction mixture was concentrated in-vacuo. Water (~50ml) was added, EtOAc (~30ml) was added and the layers partitioned, the aq layer was extracted twice more with EtOAc (~30ml) and the combined organics were evaporated to dryness under reduced pressure to give the title compound (245mg) as an off white solid. δ H (d_6 -DMSO, 400 MHz): 8.17 (2H, apparent d), 7.39 (1H, s), 4.68-4.74 (1H, m), 1.55-1.76 (2H, m), 1.31 (3H, d), 0.95 (3H, t). MS (ES): $C_{12}H_{13}NO_2$ requires 219; found 220 (MH^+).

Description for D37

5-Formyl-2-[[[(1R)-1-methylpropyl]oxy]benzonitrile (D37).

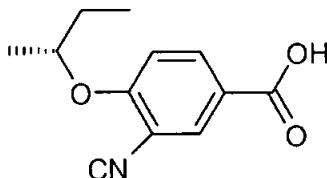
71



(2*R*)-2-Butanol (0.99 g, 0.013 mol) was dissolved in DMF (50 ml) and the solution cooled to 0 °C. To this was added sodium hydride, 60% dispersion in mineral oil (1.54g, 0.036 mol) in a portion-wise manner, the mixture was stirred at 0 °C for 10 minutes after complete addition. 2-Fluoro-5-formylbenzonitrile (2.0 g, 0.013 mol) was then added and the reaction mixture allowed to warm to room temperature (slowly within the ice bath) and the reaction mixture was stirred overnight at room temperature. The reaction mixture was then cooled to 0 °C, quenched with brine and diluted with EtOAc (~25ml). The mixture was partitioned and the organic fraction extracted with water (~30ml), the combined organics were dried by passing through a phase separating cartridge and evaporated to dryness under reduced pressure to give the crude product. The crude residue was purified on a 40+M Biotage cartridge, eluting with a 20 to 50 % mixture of EtOAc in hexane. This gave the title compound (310mg) as a yellow oil. δ H (d_6 -DMSO, 400 MHz): 9.88 (1H, s), 8.30 (1H, s), 8.15 (1H, d), 7.49 (1H, d), 4.73-4.81 (1H, m), 1.63-1.79 (2H, m), 1.33 (3H, d), 0.95 (3H, t) ppm.

Description for D38

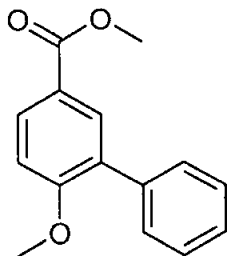
3-Cyano-4-[[*(1R)*-1-methylpropyl]oxy]benzoic acid (D38)



20

To a solution of 5-formyl-2-[[*(1R)*-1-methylpropyl]oxy]benzonitrile (**D37**) (310mg, 1.53 mmol) in acetic acid (30ml) was added sodium perborate tetrahydrate (471mg, 3.05 mmol), the reaction mixture was heated at 50 °C over the weekend. The reaction mixture was concentrated in vacuo and water (~50ml) added, EtOAc (~30ml) was added and the layers partitioned, the aq layer was extracted twice more with EtOAc (~30ml) and the combined organics evaporated to dryness under reduced pressure to give the title compound (315mg) as an off-white solid. δ H (d_6 -DMSO, 400 MHz): 8.07-8.24 (2H, m), 7.38 (1H, d), 4.63-4.77 (1H, m), 1.55-1.83 (2H, m), 1.31 (3H, d), 0.95 (3H, t). MS (ES^+): $C_{12}H_{13}NO_2$ requires 219; found 220 (MH^+).

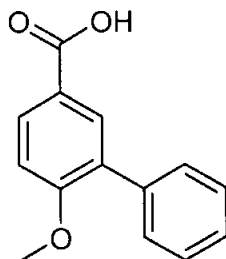
25

Description for D39**Methyl 6-(methyloxy)-3-biphenylcarboxylate (D39)**

- 5 Methyl 3-bromo-4-(methyloxy)benzoate (245 mg, 1 mmol, commercially available) was dissolved in DME : 2N Na₂CO₃ (2:1, 18 ml) and then phenyl boronic acid (244 mg) and tetrakis(triphenylphosphine) palladium(0) (58 mg) were added. The reaction was heated to 80 °C and then left to cool over the weekend. Added EtOAc and water, the organics were separated, dried and evaporated to give a black gum.
- 10 Purification by flash chromatography afforded the title compound (194 mg) as a gum. δ H (d₆-DMSO, 400MHz) 3.83 (3H, s), 3.85 (3H, s), 7.24 (1H, d), 7.33-7.50 (5H, m), 7.83 (1H, d), 7.97 (1H, dd). MS (ES): C₁₅H₁₄O₃ requires 242; found 243 (MH⁺).

Description for D40

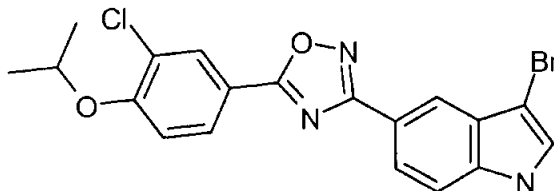
- 15 **6-(Methyloxy)-3-biphenylcarboxylic acid (D40)**



- Methyl 6-(methyloxy)-3-biphenylcarboxylate (D39) (194 mg, 0.8 mmol) dissolved in 2N NaOH aq. (3 ml) and methanol (3 ml). Stirred at room temperature overnight and then the organic solvent was evaporated in vacuo. Added EtOAc/water separated
- 20 and then acidified the aqueous and re-extracted. The organic extracts were dried and evaporated to afford 202 mg of the title compound as a white solid. δ H (d₆-DMSO, 400MHz) 3.84 (3H, s), 7.22 (1H, d), 7.33-7.49 (5H, m), 7.82 (1H, d), 7.95 (1H, dd), MS (ES⁺): C₁₄H₁₂O₃ requires 228; found 229 (M+H⁺).

- 25 **Description for D41**

3-Bromo-5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indole (D41)



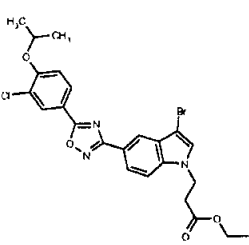
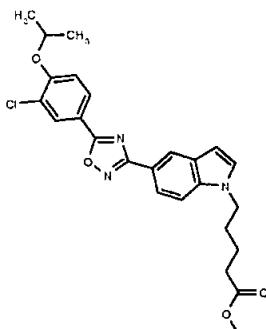
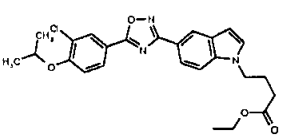
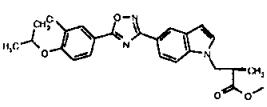
To 5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indole (**D5**) (450mg, 1.27 mmol) dissolved in DMF (12ml) was added bromine (213mg, 1.35 mmol) dropwise. Stirred for 15 minutes, evaporated off the DMF, added diethyl ether (70ml) and washed with water (2x70ml). Dried over MgSO₄ and evaporated off the solvent. The residue was crystallised from diethyl ether/hexane to give 160mg of the title compound as a white solid. δ H (400 MHz, d₆-DMSO) 1.37 (6H, d), 4.88 (1H, sept), 7.44 (1H, d), 7.59 (1H, dd), 7.72 (1H, d), 7.91 (1H, dd), 8.13-8.32 (3H, m). MS (ES) C₁₉H₁₅⁷⁹BrClN₃O₂ requires 431; found 432 (MH⁺).

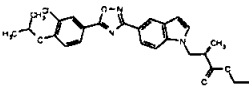
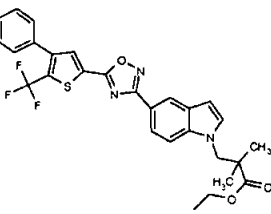
The following esters were prepared in a similar fashion to the previously described examples (such as **D6**) using the appropriate indole and alkylating agent. The alkyl halides were commercially available apart from **D11** used to prepare **D48**. Unless stated otherwise, the reactions were performed in DMF. On some occasions the reactions were worked up by an aqueous work-up procedure whilst on others the crude material was used directly in the hydrolysis step following evaporation of the reaction solvent.

20

	Structure	Name	Precursor indole	Comments	MH+
D42		ethyl (5-(5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl)acetate	D2	solvent DMPU rather than DMF. Reaction at 100-120 °C in microwave.	—

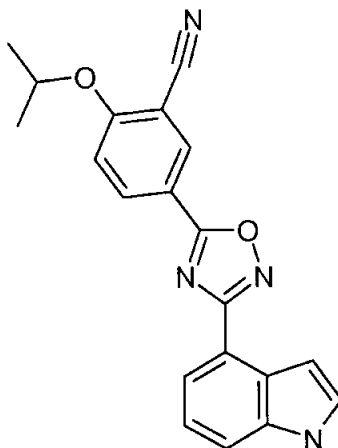
72

D43		ethyl 3-[3-bromo-5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoate	D41	Reaction conventionally heated to 80 °C	534 for ⁸¹ Br ³⁵ Cl
D44		methyl 5-[5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]pentanoate	D5	Reaction conventionally heated to 80 °C	468
D45		ethyl 4-[5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]butanoate	D5	Reaction heated in the microwave at 130 °C. Crude material used in next step following evaporation.	—
D46		methyl (2R)-3-[5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]-2-methylpropanoate	D5	Reaction heated in the microwave at 140 °C. Crude material used in next step following evaporation.	—

D47		ethyl (2S)-3-[5-(5-(3-chloro-4-[(1-methylethyl)oxy]phenyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]-2-methylpropanoate	D5	Reaction heated in the microwave at 130 °C. Crude material used in next step following evaporation.	—
D48		ethyl 2,2-dimethyl-3-(5-(5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl)propanoate	D2	Reaction heated in the microwave at 131-150 °C. Crude material used in next step following evaporation.	540

Description for D49

- 5 5-[3-(1*H*-indol-4-yl)-1,2,4-oxadiazol-5-yl]-2-[(1-methylethyl)oxy]benzonitrile (D49)



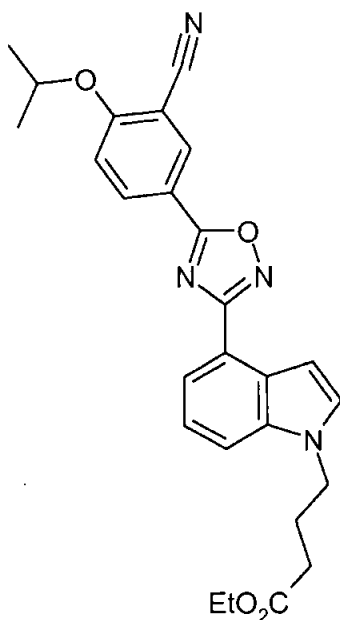
To 3-cyano-4-[(1-methylethyl)oxy]benzoic acid (can be prepared as described in WO2005/58848) (500mg, 2.44 mmol) in DMF (15ml) was added EDAC (514mg, 2.67

76

mmol) and HOBt (367 mg, 2.67 mmol) and the solution left standing for 30 minutes. Added *N*-hydroxy-1*H*-indole-4-carboximidamide (**D9**) (427 mg, 2.44 mmol) and left standing for 1 hour. To the solution were added EDAC (117mg, 0.61 mmol) and HOBt (84mg, 0.61 mmol) and left standing for 2 hours. To the solution were added
5 EDAC (234.9 mg, 1.22 mmol) and HOBt (167.7 mg, 1.22 mmol) and left standing overnight. Heated at 80 °C overnight, cooled and added EtOAc (30ml). Washed with water (30ml), sat. sodium hydrogen carbonate (30ml) and water (30ml). Dried over MgSO₄ and evaporated off the solvent. The residue was triturated with diethyl ether to give 353 mg of the title compound as a pale brown solid. δ H (400 MHz, d₆-DMSO)
10 1.39 (6H, d), 4.94-5.03 (1H, m), 7.09-7.10 (1H, m), 7.30 (1H, t), 7.56-7.59 (2H, m), 7.67 (1H, d), 7.92 (1H, dd), 8.45 (1H, dd), 8.55 (1H, d), 11.52 (1H, broad s). MS (ES) C₂₀H₁₆N₄O₂ requires 344; found 345 (MH⁺).

Description for D50

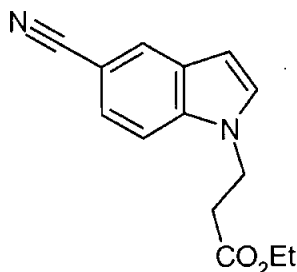
15 **Ethyl 4-[4-(5-[3-cyano-4-[(1-methylethyl)oxy]phenyl]-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]butanoate (D50)**



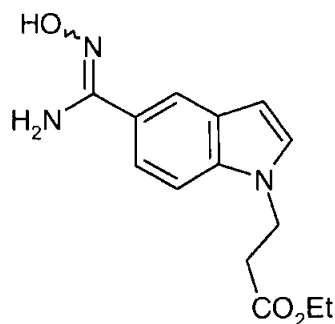
A mixture of 5-[3-(1*H*-indol-4-yl)-1,2,4-oxadiazol-5-yl]-2-[(1-methylethyl)oxy]benzonitrile (**D49**) (100mg, 0.29 mmol), ethyl 4-bromobutyrate (85
20 mg, 0.44mmol) and cesium carbonate (189mg, 0.58 mmol) in DMF (2ml) was heated at 80 °C for 1 hour. Added ethyl 4-bromobutyrate (85mg, 0.44 mmol) and heated overnight at 80 °C. Added ethyl 4-bromobutyrate (85mg, 0.44 mmol) and cesium carbonate (189 mg, 0.58 mmol) and heated for 24 hours. Added ethyl 4-

27

bromobutyrate (85 mg, 0.44 mmol) and heated for 24 hours. Added ethyl 4-bromobutyrate (85mg, 0.44 mmol) and heated for 6 hours. Added EtOAc (20ml) and washed with water (20ml). Dried over MgSO_4 and evaporated off the solvent. The residue was crystallised from ethanol to give the title compound (55 mg) as a white solid. MS (ES) $\text{C}_{26}\text{H}_{26}\text{N}_4\text{O}_4$ requires 458; found 459 (MH^+).

Description 51**Ethyl 3-(5-cyano-1H-indol-1-yl)propanoate (D51)**

- 10 A mixture of 1H-indole-5-carbonitrile (1.42g, 10 mmol), ethyl 3-bromopropanoate (1.92ml, 15 mmol) and cesium carbonate (6.5g, 20 mmol) in DMF (50ml) was heated at 80 °C for 4 hours. Cooled the solution, added diethyl ether (300ml) and washed with water (3X 300ml). Dried over MgSO_4 and evaporated off the solvent to yield 2.4g of pale orange oil. This crude product was used in the next stage (preparation of
- 15 **D52**).

Description for D52**Ethyl 3-{5-[(hydroxyamino)(imino)methyl]-1H-indol-1-yl}propanoate**

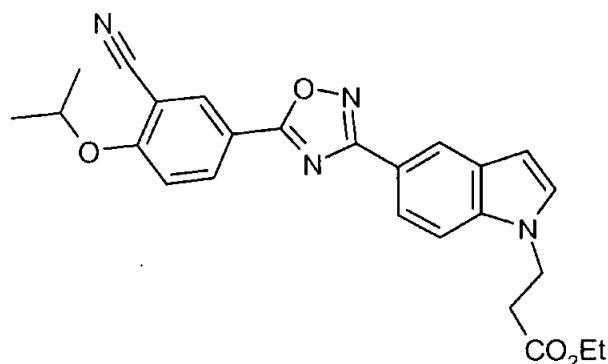
- 20 Ethyl 3-(5-cyano-1H-indol-1-yl)propanoate (**D51**) (1.7g, 7.2 mmol), hydroxylamine hydrochloride (1.0g, 14.4 mmol) and sodium hydrogen carbonate (2.42g, 28.9 mmol) were suspended in ethanol (100ml) and stirred at 50 °C for 3 days. A single product formed but 15% starting material remained. Cooled, filtered off the inorganic material and evaporated off the solvent. The product was crystallised from a mixture of

78

EtOAc, diethyl ether and hexane to yield 1.9g of the title compound as a white solid.
MS (ES) $C_{14}H_{17}N_3O_3$ requires 275; found 276. (MH^+).

Description for D53

- 5 Ethyl 3-[5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]propanoate (D53)

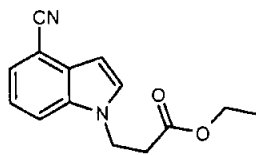


10

- 3-Cyano-4-[(1-methylethyl)oxy]benzoic acid (can be prepared as described in
WO2005/58848) (215mg, 1.05 mmol), EDAC (219mg, 1.14 mmol) and HOBt
(156mg, 1.14 mmol) in dry DMF (10ml) were stirred at RT for 10 minutes. Added
ethyl 3-[5-[(hydroxyamino)(imino)methyl]-1*H*-indol-1-yl]propanoate (D52) (288mg,
15 1.05 mmol) and stirred for 1 hour at RT. Heated at 80 °C for 7 hours. The solution
was cooled and EtOAc (50ml) added. Washed with water (50ml), sat. sodium
hydrogen carbonate (50ml) and water (50ml). Dried over $MgSO_4$ and evaporated off
the solvent. The residue was crystallised from ether to yield 200mg of the title
compound as a very pale pink solid. MS (ES) $C_{25}H_{24}N_4O_4$ requires 444; found 445
20 (MH^+)

Description for D54

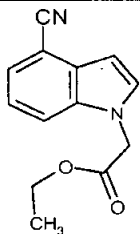
Ethyl 3-(4-cyano-1*H*-indol-1-yl)propanoate (D54)



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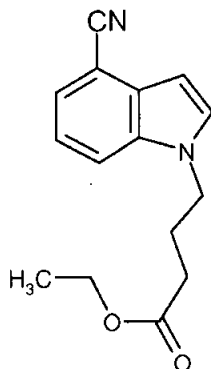
4-Cyanoindole (2.5 g) was dissolved in DMF (7.5 ml). Cs_2CO_3 (11.46 g) was added followed by ethyl 3-bromopropionate (3.38 ml). This mixture was heated to 80 °C for 40 minutes. A further portion of DMF (5 ml) was added and heating at 80 °C continued for 1 hour. The reaction mixture was evaporated then dissolved in H_2O (200 ml) and extracted with EtOAc (200 ml). This was evaporated to give a yellow oil (3.5 g) which was purified on a 40+M Biotage cartridge, eluting with a 25-75 % mixture of Et_2O in hexane. This gave the title compound (3.44 g) as a pale yellow oil. δH (CDCl_3 , 400MHz): 1.19 (3H, t), 2.82 (2H, t), 4.12 (2H, q), 4.50 (2H, t), 6.71 (1H, d), 7.23-7.28 (1H, m), 7.33 (1H, d), 7.47 (1H, d), 7.60 (1H, dd). MS (ES): $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2$ requires 242; found 243 (MH^+).

The following example was prepared by a similar method to those described above. The reaction was not complete after the work-up and so the material was resubmitted to the reaction conditions with an extra 0.2 equivalents of base and alkylating agent and the product was purified by trituration with ether.

Number	Structure	Name	MH^+
D55		ethyl (4-cyano-1H-indol-1-yl)acetate	229

Description for D56

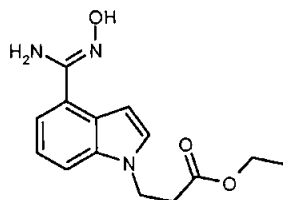
Ethyl 4-(4-cyano-1H-indol-1-yl)butanoate (D56)



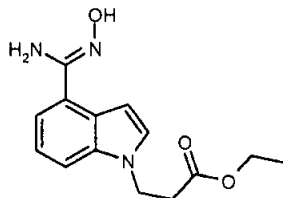
Combined 4-cyanoindole (5 g, 35.2 mmol), ethyl-4-bromobutanoate (10.29 g, 52.8 mmol) and cesium carbonate (22.92 g, 70.3 mmol) and heated to 80 °C under argon for 1 hour. The reaction was allowed to cool and then 150ml diethyl ether was added and the organic solution was washed with 3 x 150ml H₂O. Dried the organic solution over MgSO₄ and evaporated the solvent. Dried on high vacuum over the weekend to afford the title compound (8.25 g) as an orange oil. δ H (400 MHz, d₆-DMSO). 1.13 (3H, t), 1.96-2.05 (2H, m), 2.26 (2H, t), 3.99 (2H, q), 4.29 (2H, t), 6.60 (1H, dd), 7.29 (1H, apparent t), 7.55 (1H, dd), 7.68 (1H, d), 7.90 (1H, d). MS (ES): C₁₅H₁₆N₂O₂ requires 256; found 257 (MH⁺).

Description for D57

Ethyl 3-{4-[(hydroxyamino)(imino)methyl]-1H-indol-1-yl}propanoate (D57)



Ethyl 3-(4-cyano-1H-indol-1-yl)propanoate (**D54**) (3.44 g), NH₂OH.HCl (1.97 g) and Na₂CO₃ (5.96 g) were dissolved in EtOH (75 ml). This mixture was heated at 50 °C overnight. A further portion of NH₂OH.HCl (985 mg) was added and the mixture stirred at 70 °C overnight. The reaction mixture was then filtered and evaporated to give the title compound (4.06 g). MS (ES): C₁₄H₁₇N₃O₃ requires 275; found 276 (MH⁺)

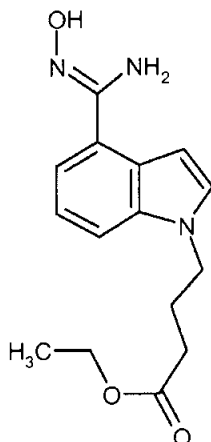
Description for D57 (alternative procedure)**Ethyl 3-{4-[(hydroxyamino)(imino)methyl]-1H-indol-1-yl}propanoate (D57)**

- A mixture of 1H-indole-4-carbonitrile (3.4 g, 23.92 mmol), ethyl 3-bromopropanoate (4.57 ml, 35.9 mmol) and cesium carbonate (15.59 g, 47.8 mmol) was heated at 80 °C for 2 hours and left standing overnight. Ether (400ml) was added and the resulting mixture was washed with water (3X400ml), dried over MgSO₄ and evaporated to yield 6.6 g of pale yellow clear oil
- The oil N4111-30-A2 (6.6 g, 27.2 mmol), hydroxylamine hydrochloride (3.79 g, 54.5 mmol) and sodium bicarbonate (9.15 g, 109 mmol) in ethanol were stirred at 50 °C overnight. Added further hydroxylamine hydrochloride (2.3g) and heated at 50 °C for 24 hours. The reaction was filtered the residue washed with DCM (50ml). The solvent was removed by evaporation and the residue triturated with hexane to obtain the title compound (4.2g) as a white solid. Further title compound (1.0 g) as a white solid was obtained from trituration of residues. Mass spectral data consistent with previous synthesis.

The following was made in a similar fashion to the first **D57** procedure listed, sodium bicarbonate was the base used and the reaction was carried out at 55 °C.

Number	Structure	precursor number	Name	MH ⁺
D58		D55	ethyl {4-[(hydroxyamino)(imino)methyl]-1H-indol-1-yl}acetate	262

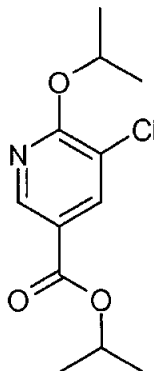
82

Description for D59**Ethyl 4-[(4-[(hydroxyamino)(imino)methyl]-1H-indol-1-yl)butanoate (D59)**

5 Ethyl 4-(4-cyano-1H-indol-1-yl)butanoate (**D56**) (8.25 g, 32.2 mmol) was dissolved in EtOH and treated with $\text{NH}_2\text{OH}\cdot\text{HCl}$ (4.47 g, 64.4 mmol) and NaHCO_3 (8.11 g, 97 mmol) and heated to 55°C for 1 day and two nights. Further $\text{NH}_2\text{OH}\cdot\text{HCl}$ (500 mg) and NaHCO_3 (500 mg) were added and the reaction was heated for another 3 hours and then separated the inorganics by filtration, washing well with EtOH. The solvent was evaporated and the residue dried under high vacuum. Trituration with ether and

10 dcm afforded two batches of the title compound N2668-20-A8 (5.14 g) and N2668-20-A9 (976 mg). δH (400 MHz, d_6 -DMSO) 1.15 (3H, t), 1.98 (2H, apparent quin), 2.25 (2H, t), 4.03 (2H, q), 4.21 (2H, t), 5.73 (2H, br s), 6.82 (1H, dd), 7.15 (1H, apparent t), 7.27 (1H, dd), 7.35 (1H, d), 7.51 (1H, d), 9.58 (1H, br s). MS (ES): $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_3$ requires 289; found 290 (MH^+).

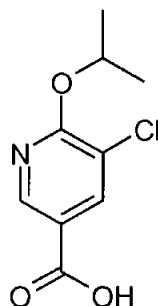
15

Description for D60**1-Methylethyl 5-chloro-6-[(1-methylethyl)oxy]-3-pyridinecarboxylate (D60)**

The 5-chloro-6-hydroxy-3-pyridinecarboxylic acid (1g, 5.76 mmol) was suspended in toluene (200ml) and treated with silver carbonate (3.97 g, 14.40 mmol) and 2-iodopropane (3.46 ml, 34.6 mmol) and stirred at RT in the dark for 3 days. LC/MS showed 2/3 product. Added 2-iodopropane (3ml) and stirred for 24 hours. LC/MS showed 80% product. Added EtOAc (200ml) and washed with water (200ml) + sat. NaHCO₃ (50ml) followed by water (200ml). Dried over MgSO₄ and evaporated off the solvent to yield 1.0g of the title compound as a clear, colourless oil. MS (ES⁺) C₁₂H₁₆³⁵ClNO₃ requires 257; found 257.

10 **Description for D61**

5-Chloro-6-[(1-methylethyl)oxy]-3-pyridinecarboxylic acid (D61)

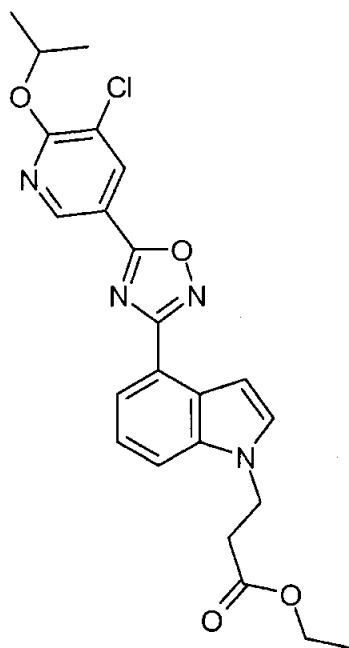


1-methylethyl 5-chloro-6-[(1-methylethyl)oxy]-3-pyridinecarboxylate (**D60**) (1.6 g, 6.21 mmol) in isopropanol (70 ml) and water (35.0 ml) was treated with 2N sodium hydroxide (6.21 ml, 12.42 mmol) and stirred for 3 hours to give a single product. Evaporated off the IPA, acidified with glacial acetic acid and extracted product into EtOAc (100ml). Dried over MgSO₄ and evaporated off the solvent to yield 1.30 g of the title compound as a white solid. MS (ES) C₉H₁₀³⁵ClNO₃ requires 215; found 214 (M-H⁺).

84

Description for D62

Ethyl 3-[4-(5-{5-chloro-6-[(1-methylethyl)oxy]-3-pyridinyl)-1,2,4-oxadiazol-3-yl]-1H-indol-1-yl]propanoate (D62)

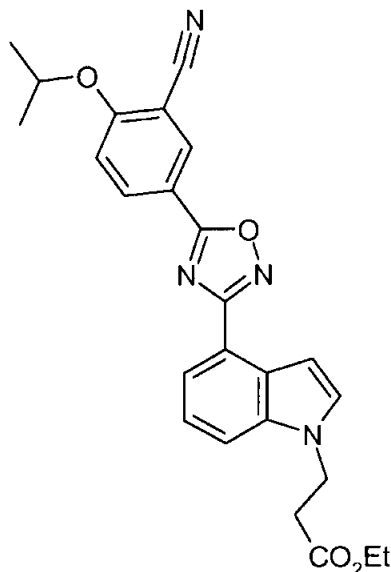


- 5 To 5-chloro-6-[(1-methylethyl)oxy]-3-pyridinecarboxylic acid (**D61**) (1.504 g, 6.97 mmol) in dry DMF (30ml) was added EDC (1.604 g, 8.37 mmol) and HOBT (1.282 g, 8.37 mmol). Stirred solution at RT for 10 minutes then added ethyl 3-[4-[(hydroxyamino)(imino)methyl]-1H-indol-1-yl]propanoate (N4111-31-A4) (**D57**) (1.92 g, 6.97 mmol). The mixture was stirred for 30 minutes. LC/MS showed one product
- 10 (intermediate). The solution was heated at 80 °C for 2 hours. Left standing overnight at RT then heated 80 °C for further 2 hours to give complete reaction. Cooled and added EtOAc (250ml). The EtOAc was washed with sat. NaHCO₃ (150ml) followed by water (2X 200ml). Dried over MgSO₄ and evaporated off the solvent. The residue was subjected to chromatography on the biotage (EtOAc/hexane 1:2). On
- 15 evaporation of most of the solvent from clean fractions and addition of hexane a white precipitate was formed. The solid was filtered off to obtain 1.1 g of the title product. MS (ES) C₂₃H₂₃³⁵ClN₄O₄ requires 454; found 455 (MH⁺).

85

Description for D63

Ethyl 3-[4-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]propanoate (D63)

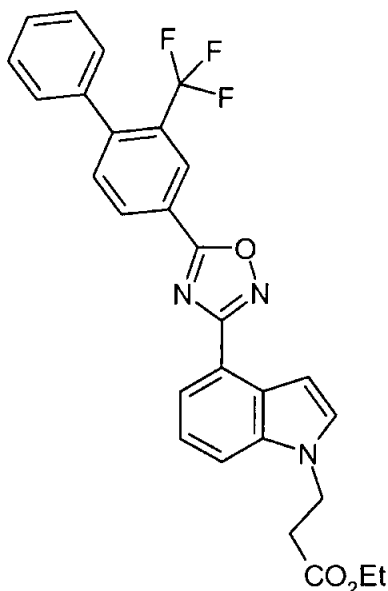


5 The 3-cyano-4-[(1-methylethyl)oxy]benzoic acid (can be prepared as described in WO2005/58848) (113mg, 0.55mmol), EDAC (115mg, 0.60 mmol) and HOBt (82mg, 0.60 mmol) were dissolved in DMF (5ml) and left standing for 15 minutes. Added ethyl 3-[4-[(hydroxyamino)(imino)methyl]-1*H*-indol-1-yl]propanoate (**D57**) (150mg, 10 0.55 mmol) and stood overnight at RT. Heated solution at 80 °C for 2 hours. LC/MS showed mostly product. After heating for a few more hours there was no change. Added EtOAc (20ml) and washed with water (30ml). Washed with saturated sodium hydrogen carbonate (30ml) and water (2X 30ml). Dried over MgSO₄ and evaporated off the solvent to obtain 81 mg of the title compound as a pale brown solid. MS (ES) 15 C₂₅H₄₄N₄O₄ requires 444; found 445 (MH⁺).

20

Description for D64

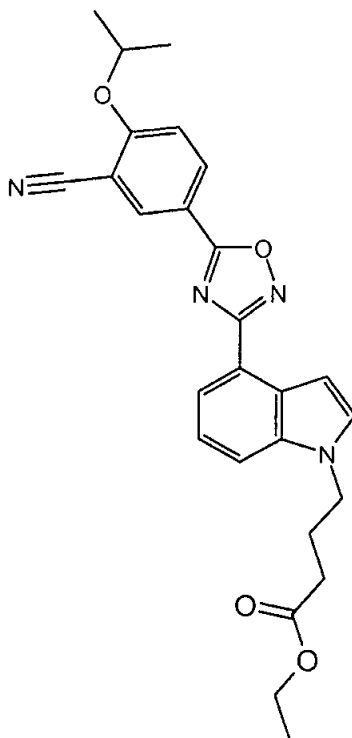
Ethyl 3-(4-{5-[2-(trifluoromethyl)-4-biphenyl]-1,2,4-oxadiazol-3-yl}-1*H*-indol-1-yl)propanoate (D64)



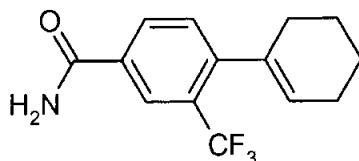
- 5 To 2-(trifluoromethyl)-4-biphenylcarboxylic acid (**D29**) (146mg, 0.55mmol) in DMF (5ml) was added EDC (115mg, 0.60 mmol) and HOBt (82mg, 0.60 mmol) and the solution left standing for 15 minutes. Added ethyl 3-{4-[(hydroxyamino)(imino)methyl]-1*H*-indol-1-yl}propanoate (**D57**) (150mg, 0.55 mmol) and stirred at RT for 1 hour. Heated at 80 °C for 1 hour then heated overnight.
- 10 Cooled then added EtOAc (20ml). Washed with water (20ml), sat aqueous sodium hydrogen carbonate (20ml) and water (20ml). Dried over MgSO₄ then evaporated of the solvent. The residue was triturated with ethanol to give 157 mg of the title compound as a white solid. δ H (400 MHz, *d*₆-DMSO) 1.11 (3H, t), 2.90 (2H, t), 4.02 (2H, q), 4.55 (2H, t), 7.10 (1H, d), 7.32-7.48 (3H, m), 7.49-7.61 (3H, m), 7.61 (1H, d), 7.73-7.84 (2H, m), 8.00 (1H, d), 8.53-8.56 (2H, m). MS (ES) C₂₈H₂₂F₃N₃O₃ requires 505; found 506 (MH⁺).
- 15

Description for D65 (alternative to description for D50)

Ethyl 4-[4-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]butanoate (D65)



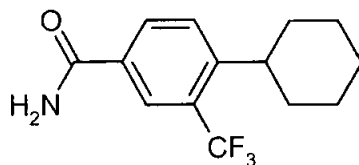
- 5 A mixture of 3-cyano-4-[(1-methylethyl)oxy]benzoic acid (can be prepared as described in WO2005/58848) (1.21g, 5.88 mmol), EDC (1.35g, 7.05 mmol) and HOBt (1.08g, 7.05 mmol) in dry DMF (85 ml) was stirred for 20 minutes at RT. Added ethyl 4-[4-[(hydroxyamino)(imino)methyl]-1*H*-indol-1-yl]butanoate (**D59**) (1.70g, 5.88 mmol) and stirred at RT for 1 hour. Heated mixture at 80 °C for 5 hours and left
- 10 overnight at RT. Heated at 80 °C for 6 hours then evaporated off the DMF. Added EtOAc (200ml) and washed with sat. NaHCO₃ (200ml) and water (200ml). Dried over MgSO₄ and evaporated off the solvent. Subjected the residue to chromatography using the biotage (EtOAc/hexane 1:2) and evaporated the cleanest fractions to yield 1.42g the title compound as a white solid. δ H (400 MHz, d₆-DMSO) 1.15 (3H, t), 1.39
- 15 (6H, d), 2.04 (2H, apparent quintet), 2.24 (2H, t), 4.00 (2H, q), 4.31 (2H, t), 4.94-5.04 (1H, m), 7.10 (1H, dd), 7.31 (1H, t), 7.56-7.60 (2H, m), 7.77 (1H, d), 7.95 (1H, d), 8.45 (1H, dd), 8.56 (1H, d). MS (ES) C₂₆H₂₆N₄O₄ requires 458; found 459 (MH⁺).

**Description for D66****4-(1-Cyclohexen-1-yl)-3-(trifluoromethyl)benzamide (D66)**

5 4-bromo-3-(trifluoromethyl)benzonitrile (commercial) (1.2 g, 4.80 mmol), 1-cyclohexen-1-ylboronic acid (0.907 g, 7.20 mmol), sodium methoxide (0.778 g, 14.40 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.337 g, 0.480 mmol) were added to dry methanol (12 mL) and the mixture heated in the microwave at 80 °C for
10 10 minutes. The reaction mixture was partitioned between ethyl acetate (40 mL) and water (40 mL) and then the organic phase washed with further water (40 mL). The organic phase was dried (MgSO₄), filtered and the solvent removed *in vacuo*. The crude product was purified by flash silica chromatography, eluting with 0-75 % ethyl acetate in hexane to give the title compound as a white solid (1.02 g). ¹H (CDCl₃,
15 400 MHz): 8.09 (1H, m), 7.90 (1H, dd), 7.32 (1H, d), 6.3-5.8 (2H, m), 5.61 (1H, s), 2.25-2.13 (4H, m), 1.80-1.60 (4H, m). MS (ES): C₁₄H₁₄F₃NO requires 269; found 270 (MH⁺).

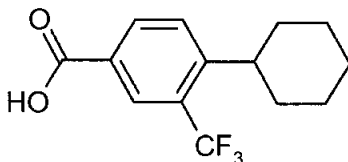
Description for D67

20 **GSK1929583A, N2123-11-A2**

4-(1-Cyclohexen-1-yl)-3-(trifluoromethyl)benzamide (D67)

25 4-(1-Cyclohexen-1-yl)-3-(trifluoromethyl)benzamide (**D66**) (850 mg, 3.16 mmol) was dissolved in methanol (63 ml) and hydrogenated using an H-Cube, using palladium on carbon at 40 °C with a flow rate of 2 mL/min. The solvent was removed *in vacuo* to give the title compound as a white solid (822 mg). ¹H (CDCl₃, 400 MHz): 8.08 (1H, d), 7.94 (1H, dd), 7.52 (1H, d), 6.54 (2H, brs), 2.97 (1H, m), 1.90-1.75 (5H, m), 1.50-1.22 (5H, m). MS (ES): C₁₄H₁₆F₃NO requires 271; found 272 (MH⁺).

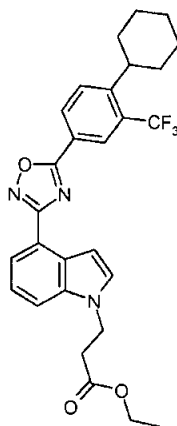
89

Description for D68**4-Cyclohexyl-3-(trifluoromethyl)benzoic acid (D68)**

5

To a solution of 4-cyclohexyl-3-(trifluoromethyl)benzamide (**D67**) (822 mg, 3.03 mmol) in ethanol (40 ml) was added potassium hydroxide (1.700 g, 30.3 mmol) and water (5 ml) and the reaction heated to 90 °C block temperature for 3 h and stirred at room temperature for 16 h. Further potassium hydroxide (1.700 g, 30.3 mmol) was added and the reaction heated at reflux for 27 h. A further 5 mL of water was added and the reaction heated for 66 hours (weekend). The reaction mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate (25 mL) and aqueous hydrochloric acid (2M, 25 mL). The aqueous layer was further extracted with ethyl acetate (25 mL) and the combined organic phases dried (MgSO₄), filtered and the solvent removed *in vacuo* to give the title compound as a white solid (737 mg). δ H (methanol-d₄, 400 MHz): 8.24 (1H, d), 8.18 (1H, dd), 7.68 (1H, d), 2.98 (1H, t), 1.72-1.95 (5H, m), 1.30-1.58 (5H, m). MS (ES): C₁₄H₁₅F₃O₂ requires 272; found 271 (M-H⁺).

20

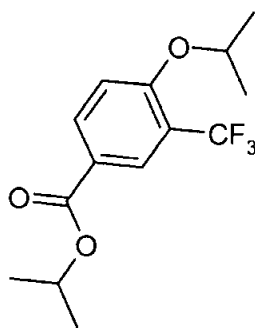
Description for D69**Ethyl 3-(4-{5-[4-cyclohexyl-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate (D69)**

90

A solution of 4-cyclohexyl-3-(trifluoromethyl)benzoic acid (**D68**) (148 mg, 0.545 mmol), EDC (115 mg, 0.599 mmol) and HOBt (92 mg, 0.599 mmol) in DMF (5 ml) was stirred for 10 min before addition of ethyl 3-{4-[(hydroxyamino)(imino)methyl]-1H-indol-1-yl}propanoate (**D57**) (150 mg, 0.545 mmol). The reaction was stirred for 30 min at room temperature followed by 16 h at 80 °C. The reaction mixture was partitioned between ethyl acetate (25 mL) and water (25 mL) and the organic phase washed with aqueous sodium bicarbonate (25 mL) and then water (25 mL). The organic phase was dried (phase separator) and the solvent removed *in vacuo*. The crude product was purified by MDAP. Some of the mixture submitted for MDAP had precipitated and was triturated with ethanol and filtered. The white solids were combined to give the title compound (63 mg). MS (ES): C₂₈H₂₈F₃N₃O₃ requires 511; found 512 (MH⁺).

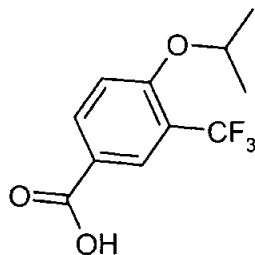
Description for D70

15 **1-Methylethyl 4-[(1-methylethyl)oxy]-3-(trifluoromethyl)benzoate (D70)**



A mixture of 4-hydroxy-3-(trifluoromethyl)benzoic acid (commercial) (450 mg, 2.18 mmol), 2-iodopropane (435 µL, 4.36 mmol) and potassium carbonate (603 mg, 4.36 mmol) in N,N'-dimethylformamide (40 mL) was heated at 70 °C for 4 h before further 2-iodopropane (218 µL, 2.18 mmol) was added and the heating continued for 18 h. The inorganic solid was filtered off and rinsed with ethyl acetate. The filtrate was concentrated *in vacuo* and partitioned between ethyl acetate (150 mL) and water (150 mL) containing some aqueous sodium hydroxide. The organic layer was dried (phase separator) and concentrated *in vacuo* to give the crude title compound (704 mg) as a yellow oil. MS (ES): C₁₄H₁₇F₃O₃ requires 290; found 291 (MH⁺).

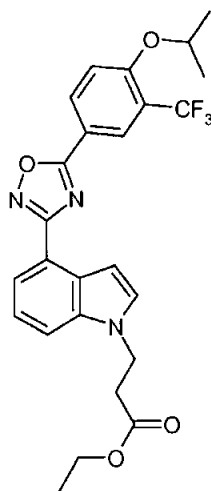
a1

Description for D71**4-[(1-Methylethyl)oxy]-3-(trifluoromethyl)benzoic acid (D71)**

5

To a mixture of 1-methylethyl 4-[(1-methylethyl)oxy]-3-(trifluoromethyl)benzoate (**D70**) (704 mg, 2.43 mmol) in ethanol (110 mL) was added aqueous sodium hydroxide (2M, 12.2 mL, 24.3 mmol) and the reaction heated to reflux for 1 h. The mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate (100 mL) and water (100 mL) and acidified with aqueous hydrochloric acid (2M, 13 mL). The aqueous layer was extracted further with ethyl acetate (100 mL) and the combined organic layers dried and concentrated *in vacuo* to give the title compound as a yellow solid (563 mg). δ H (methanol- d_4 , 400 MHz): 8.21-8.17 (2H, m), 7.26 (1H, d), 4.84 (1H, septet), 1.38 (6H, d). MS (ES): $C_{11}H_{11}F_3O_3$ requires 248; found 247 (M- H^+).

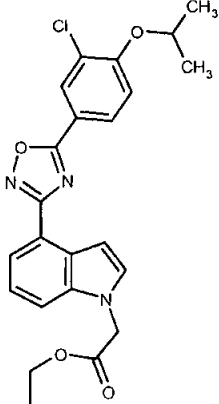
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Description for D72**Ethyl 3-(4-{5-[4-[(1-methylethyl)oxy]-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate (D72)**

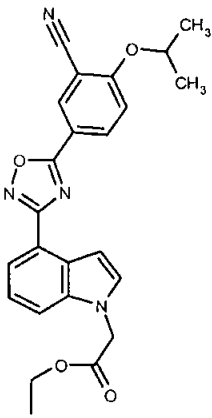
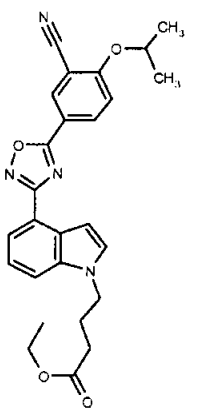
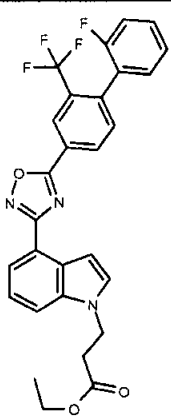
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92

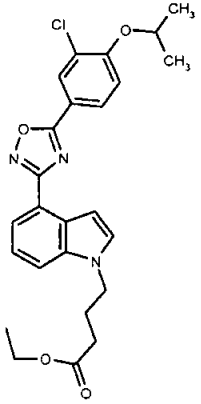
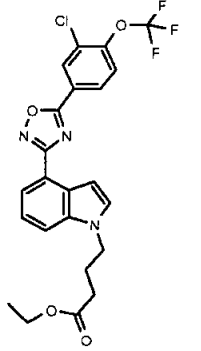
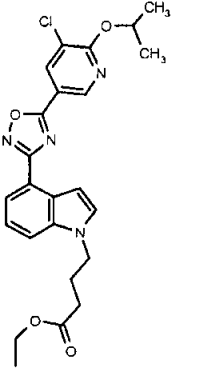
- 4-[(1-Methylethyl)oxy]-3-(trifluoromethyl)benzoic acid (**D71**) (136 mg, 0.55 mmol), EDC (116 mg, 0.61 mmol) and HOBt (82 mg, 0.61 mmol) were stirred in N,N-dimethylformamide (5 mL) for 20 min. Ethyl 3-{4-[(hydroxyamino)(imino)methyl]-1H-indol-1-yl}propanoate (**D57**) (150 mg, 0.55 mmol) was added and the reaction stirred at room temperature for 3 h and then 80 °C for 18 h. The reaction mixture was partitioned between ethyl acetate (25 mL) and water (25 mL). The organic layer was washed with aqueous sodium bicarbonate (25 mL) and water (25 mL) before it was dried (phase separator), filtered and concentrated *in vacuo*. The residue was triturated with ethanol to give the title compound (85 mg). δ H (d_6 -DMSO, 400 MHz): 8.44 (1H, dd), 8.35 (1H, d), 7.95 (1H, d), 7.81 (1H, d), 7.62-7.58 (2H, m), 7.36 (1H, app. t), 7.07 (1H, d), 4.99 (1H, septet), 4.54 (2H, t), 4.02 (2H, q), 2.89 (2H, t), 1.36 (6H, d), 1.11 (3H, t). MS (ES^+): $C_{25}H_{24}F_3N_3O_4$ requires 487; found 488 (MH^+).
- The following examples were prepared in a similar fashion to those described above. On occasion additional EDAC was required (up to 2.6 equiv) and in the case of **D80** it was necessary to elevate the temperature to 120 °C. Workup was either aqueous or alternatively the solvent was removed in *vacuo*. In the case of **D92** ethanol was added to the reaction mixture and the resultant precipitate was filtered. The compounds were purified either by trituration, MDAP, normal or reversed phase chromatography.

	Structure	Precursors	Name	MH^+
D73		D58 & D4	ethyl [4-(5-(3-chloro-4-[(1-methylethyl)oxy]phenyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]acetate	440/ 442

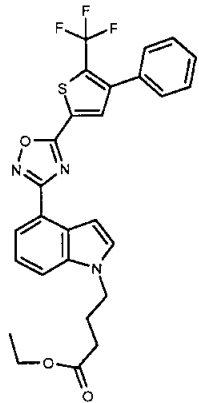
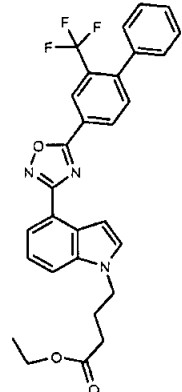
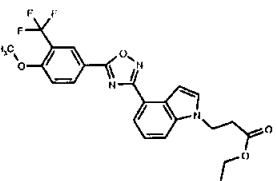
93

D74		D58	ethyl 4-(5-(3-cyano-4-[(1-methylethyl)oxy]phenyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]acetate	431
D75		D59	ethyl 4-[4-(5-(3-cyano-4-[(1-methylethyl)oxy]phenyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]butanoate	459
D76		D57 & D30	ethyl 3-(4-{5-[2'-fluoro-2-(trifluoromethyl)-4-biphenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate	524

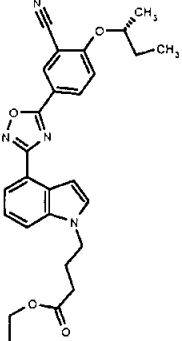
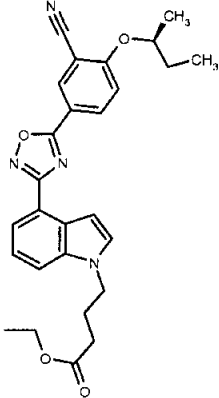
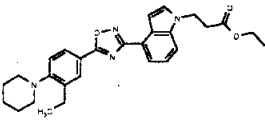
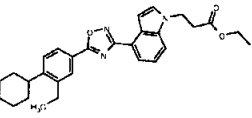
44

D77		D59 & D4	ethyl 4-[4-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]butanoate	468
D78		D59	ethyl 4-[4-(5-{3-chloro-4-[(trifluoromethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]butanoate	494
D79		D59 & D61	ethyl 4-[4-(5-{5-chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]butanoate	469

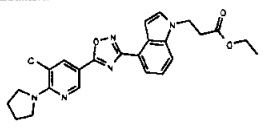
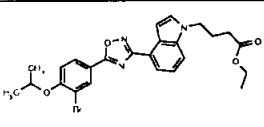
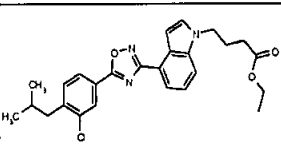
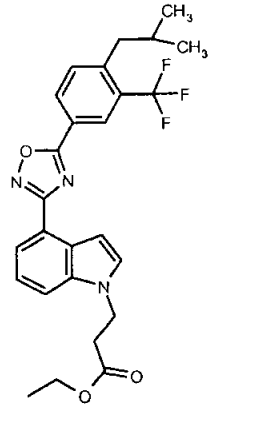
1

D80		D59	ethyl 4-(4-(5-(4-phenyl-5-(trifluoromethyl)-2-thienyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl)butanoate	526
D81		D59 & D29	ethyl 4-(4-(5-(2-(4-biphenyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl)butanoate	520
D82		D57	ethyl 3-(4-(5-(4-(methoxy)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl)propanoate	460

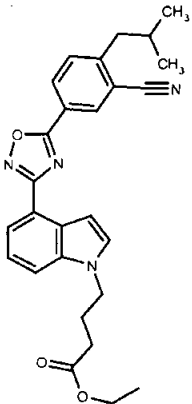
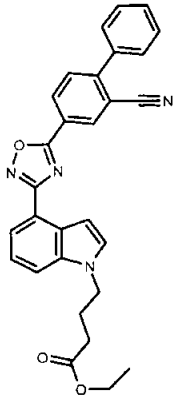
96

D83		D59 & D38	ethyl 4-{4-[5-(3-cyano-4- {[(1R)-1-methylpropyl]oxy}phenyl)- 1,2,4-oxadiazol-3-yl]-1H- indol-1-yl}butanoate	473
D84		D59 & D36	ethyl 4-{4-[5-(3-cyano-4- {[(1S)-1-methylpropyl]oxy}phenyl)- 1,2,4-oxadiazol-3-yl]-1H- indol-1-yl}butanoate	473
D85		D57 & D13	ethyl 3-(4-{5-[3-ethyl-4-(1- piperidinyl)phenyl]-1,2,4- oxadiazol-3-yl}-1H-indol- 1-yl)propanoate	473
D86		D57 & D19	ethyl 3-(4-{5-[4-(4-cyclohexyl-3- ethylphenyl)-1,2,4- oxadiazol-3-yl]-1H-indol- 1-yl}propanoate	472

97

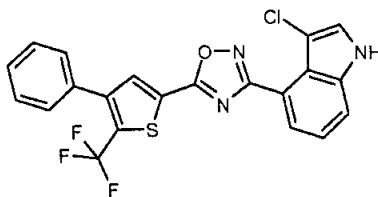
D87		D57 & D15	ethyl 3-(4-(5-(5-chloro-6-(1-pyrrolidinyl)-3-pyridinyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl)propanoate	466
D88		D59 & D21	ethyl 4-(4-(5-(3-bromo-4-((1-methylethyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl)butanoate	512
D89		D59 & D24	ethyl 4-(4-(5-(3-chloro-4-(2-methylpropyl)phenyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl)butanoate	466
D90		D57 & D34	ethyl 3-(4-(5-(4-(2-methylpropyl)-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl)propanoate	486

Cp8

D91		D59 & D32	ethyl 4-(4-{5-[3-cyano-4-(2-methylpropyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)butanoate	457
D92		D59 & D27	ethyl 4-(4-[5-(2-cyano-4-biphenyl)-1,2,4-oxadiazol-3-yl]-1H-indol-1-yl)butanoate	477

Description for D93

3-Chloro-4-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1H-indole (D93)

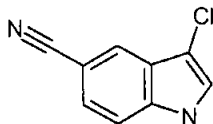


5

This material was prepared in a similar fashion to **D7** (CQ107723-108A2) from **D10** except that the reaction was stirred for four hours rather than overnight. MS (ES): $C_{21}H_{11}ClF_3N_3OS$ requires 445; found 446 (MH^+).

10

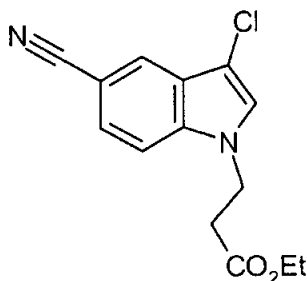
99

Description for D94**3-Chloro-1H-indole-5-carbonitrile (D94)**

5

To a solution of 5-cyanoindole (3.0g, 21mmol) in dry DMF (50ml) was added *N*-chlorosuccinimide (2.94g, 22 mmol) and the solution stirred at room temperature for 1 hour. The solution was left standing over the weekend. LC/MS showed a single product. Added ethyl acetate (150ml) and diethyl ether (50ml) and washed with water
10 (3X 300ml). Dried over MgSO₄ and evaporated off the solvent to yield 3.9 g of the title compound as a pale yellow solid. δ H (400 MHz, d₆-DMSO) 7.54 (1H, dd), 7.61 (1H, dd), 7.78 (1H, d), 8.01-8.02 (1H, m), 12.2 (1H, broad s). MS (from LCMS of reaction mixture) (ES):C₉H₅ClN₂ requires 176; found 177 (MH⁺).

15

Description for D95**Ethyl 3-(3-chloro-5-cyano-1H-indol-1-yl)propanoate (D95)**

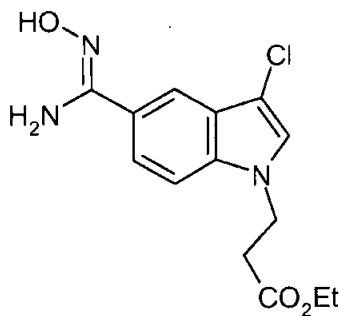
A mixture of 3-chloro-1H-indole-5-carbonitrile (**D94**) (1.8g, 10mmol), ethyl-3-bromopropionate (1.92ml, 15mmol), cesium carbonate (6.5g, 20mmol) and DMF
20 (50ml) was heated at 80 °C for 4 hours to give complete reaction. After allowing mixture to cool to room temperature diethyl ether (300ml) was added and the solution washed with water (3X300ml). Dried over MgSO₄ and evaporated off the solvent to give a brown solid. The solid was triturated with a mixture of diethyl ether and hexane to obtain 2.5g of the title compound as a tan solid. Crude product used
25 in the next stage (synthesis of **D96**).

100

Description for D96

Ethyl 3-[3-chloro-5-(hydroxyamino)(imino)methyl]-1H-indol-1-yl]propanoate (D96)

5

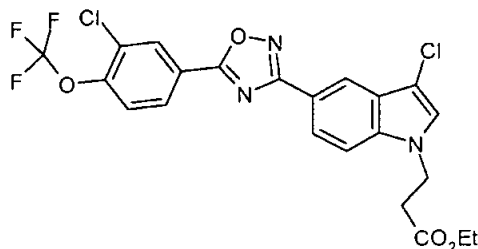


- 10 A mixture of ethyl 3-(3-chloro-5-cyano-1H-indol-1-yl)propanoate (**D95**) (2.0g, 7.2 mmol), hydroxylamine hydrochloride (1.0g, 14.4 mmol), sodium hydrogen carbonate (2.42g, 28.9 mmol) and ethanol (100ml) was heated at 50 °C over the weekend. Still 25% starting material present by LC/MS. Added hydroxylamine hydrochloride (0.5g, 7.2 mmol) and sodium hydrogen carbonate (1.2g, 14.3 mmol) and heated at 50 °C
- 15 for 24 hours. There was only a small amount of starting material present so it was decided to work up the reaction. The inorganic material was filtered off. The solvent was evaporated and the residue triturated using ethyl acetate and diethyl ether to yield 1.9 g of the title compound as a pale yellow solid. MS (ES) $C_{14}H_{16}ClN_3O_3$ requires 309; found 310 (MH^+).

20

Description for D97

Ethyl 3-[3-chloro-5-(5-[3-chloro-4-[(trifluoromethyl)oxy]phenyl]-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoate (**D97**)

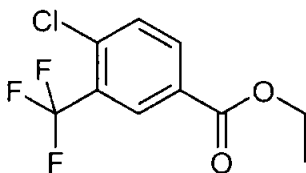


25

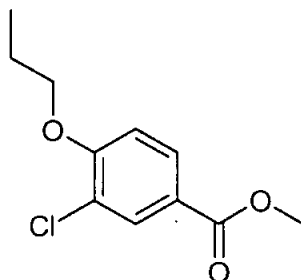
3-Chloro-4-[(trifluoromethyl)oxy]benzoic acid (commercial: ABCR) (168mg, 0.70 mmol) stirring in DMF (6ml) was treated with EDC (146mg, 0.76 mmol) followed by HOBt (104mg, 0.76 mmol). The resultant solution was stirred for 15 minutes. Added ethyl 3-{3-chloro-5-[(hydroxyamino)(imino)methyl]-1H-indol-1-yl}propanoate (D96) (216mg, 0.70 mmol) and stirred at RT for 45 minutes. The solution was heated at 80 °C for 6 hours then left standing at room temperature overnight. Single product formed by LC/MS. Added EtOAc (50ml) and washed with water (50ml), saturated aqueous sodium hydrogen carbonate (50ml) and water (50ml). Dried over MgSO₄ and evaporated off the solvent. The residue was crystallised from ethanol to yield 200mg of white solid. δ H (400 MHz, d₆-DMSO) 1.11 (3H, t), 2.92 (2H, t), 4.00 (2H, q), 4.49 (2H, t), 7.75 (1H, s), 7.80 (1H, d), 7.85 (1H, dd), 7.95 (1H, dd) 8.23 (1H, d) 8.30 (1H, dd), 8.47 (1H, d). MS (ES) C₂₂H₁₆³⁵Cl³⁷ClF₃N₃O₄ requires 515; found 516 (MH⁺).

Description for D98 (alternative to description for D28)

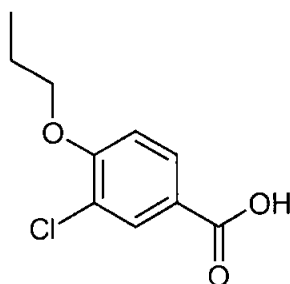
Ethyl 4-chloro-3-(trifluoromethyl)benzoate (D98)



A solution of 4-chloro-3-trifluoromethyl benzoic acid (10 g, 44.5 mmol) in ethanol (10 ml) was split equally between two microwave vials. Concentrated sulfuric acid (0.75 ml) was added to each vial (1.5 ml in total). The reactions were heated in the microwave at 120 °C for 30 minutes in total. The reaction mixtures were combined and concentrated *in vacuo*. The residue was partitioned between EtOAc (100 ml) and aq. sodium bicarbonate (100 ml), the organic phase was separated, washed with aq. sodium bicarbonate (100 ml) and water (2 x 100 ml) and then dried (phase separator) and the solvent removed *in vacuo* to give the title compound (4.126 g) as a colourless oil. δ H (400 MHz, methanol-d₄) 1.40 (3H, t), 4.41 (2H, quart), 7.76 (1H, d), 8.22 (1H, dd), 8.34 (1H, d).

Description for D99**Methyl 3-chloro-4-(propyloxy)benzoate (D99)**

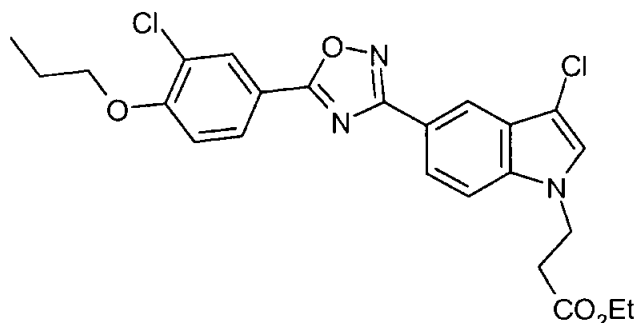
Methyl 4-hydroxy-3-chlorobenzoate (10 g, 53.6 mmol) was dissolved in DMF (110 ml) and then potassium carbonate (14.8 g, 107.2 mmol) was added followed by n-propyliodide (10.4 ml, 107.2 mmol). The reaction was heated to 70 °C overnight, filtered and then the filtrate was partitioned between EtOAc and water. The organic layer was separated, dried and evaporated to give the title compound as a yellow oil (12.37 g). δ H (400 MHz, d_6 -DMSO) 1.00 (3H, t), 1.72-1.92 (2H, m), 3.82 (3H, s), 4.10 (2H, t), 7.24 (1H, d), 7.85-8.10 (2H, m). MS (ES) $C_{11}H_{13}^{35}ClO_3$ requires 228; found 229 (MH^+).

Description for D100**3-Chloro-4-(propyloxy)benzoic acid (D100)**

A solution of methyl 3-chloro-4-(propyloxy)benzoate (**D99**) (12.22 g, 0.053 mol) in ethanol (40 ml) and 2M NaOH aq. (40 ml) was heated at 60 °C for 3 hours. The reaction was allowed to cool and then left at room temperature over the weekend. The reaction mixture was poured into a mixture of dilute aq. HCl and EtOAc. The organic layer was separated, dried and evaporated to give a solid which was triturated with ether to give the title compound as a white solid (7.7 g). δ H (400 MHz, d_6 -DMSO) 1.00 (3H, t), 1.67-1.87 (2H, m), 4.10 (2H, t), 7.24 (1H, d), 7.84-8.06 (2H, m), 12.97 (1H, br s). MS (ES) $C_{10}H_{11}^{35}ClO_3$ requires 214; found 213 ($M-H^+$).

Description for D101

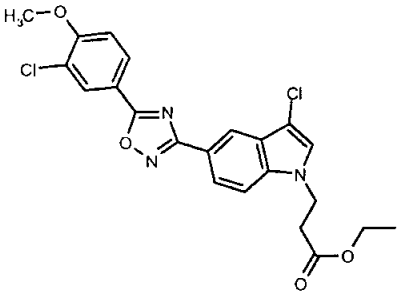
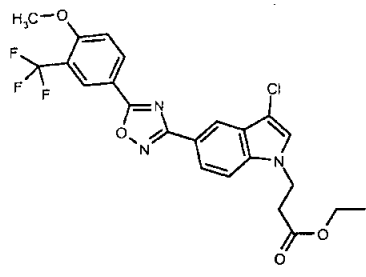
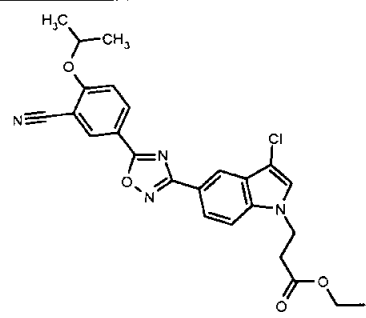
Ethyl 3-(3-chloro-5-{5-[3-chloro-4-(propyloxy)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate (D101)

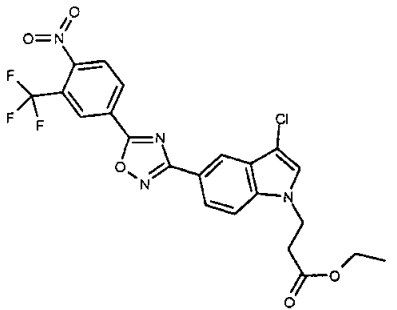


- 5 3-Chloro-4-(propyloxy)benzoic acid (**D100**) (150mg, 0.70 mmol) stirring in DMF was treated with EDC (146mg, 0.76 mmol) followed by HOBt (104mg, 0.76 mmol). The resultant solution was stirred and ethyl 3-{3-chloro-5-[(hydroxyamino)(imino)methyl]-1H-indol-1-yl}propanoate (**D96**) (216mg, 0.70 mmol) added. Heated mixture at 80 °C until reaction was complete. Work up obtained the title compound as 160 mg of pale cream solid. δ H (400 MHz, d_6 -DMSO) 1.03 (3H, t), 1.10 (3H, t), 1.77-1.86 (2H, m), 2.90 (2H, t), 4.05 (2H, q), 4.18 (2H, t), 4.49 (2H, t), 7.40 (1H, d), 7.74 (1H, s), 7.81 (1H, d), 7.91 (1H, dd), 8.15 (1H, dd), 8.22-8.23 (2H, m). MS (ES) $C_{24}H_{23}^{35}Cl_2N_3O_4$ requires 487; found 488 (MH^+).
- 10
- 15 The following compounds were prepared by similar methods to those described above. The reactions were worked up by partitioning the crude material between ethyl acetate and aq. sodium bicarbonate, separating the organic layer, drying it and evaporating to dryness. The compounds were purified by trituration or normal phase chromatography.
- 20

	Structure	precursor	Name	MH^+

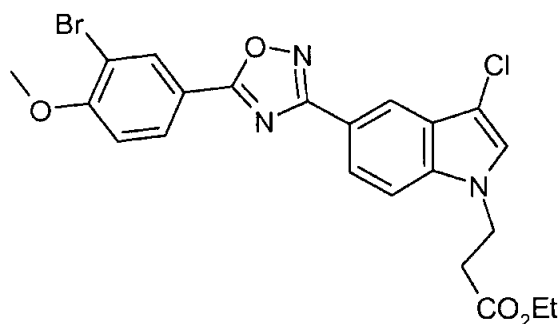
104

D102		D96	ethyl 3-(3-chloro-5-{[3-chloro-4-(methoxy)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate	460
D103		D96	ethyl 3-(3-chloro-5-{[4-(methoxy)-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate	494
D104		D96	ethyl 3-[3-chloro-5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoate	479

D105		D96	ethyl 3-(3-chloro-5-{5-[4-nitro-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate	-
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Description for D106

Ethyl 3-(5-{5-[3-bromo-4-(methoxy)phenyl]-1,2,4-oxadiazol-3-yl}-3-chloro-1H-indol-1-yl)propanoate (D106)

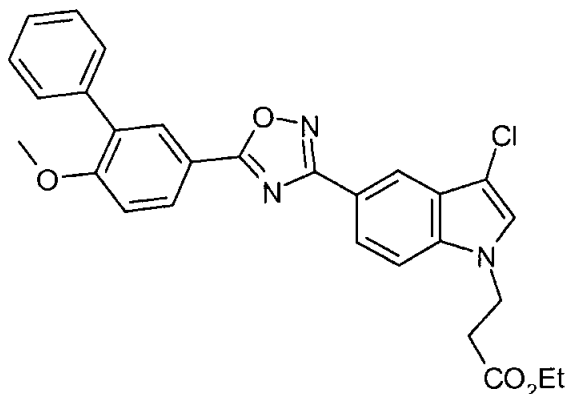


5

- The 3-bromo-4-(methoxy)benzoic acid (commercial: ICN) (243mg, 1.05 mmol) stirring in DMF (10ml) was treated with EDC (219mg, 0.1.14 mmol) followed by HOBT (156mg, 0.1.14 mmol). The resultant solution was stirred for 10 minutes. Added ethyl 3-{3-chloro-5-[(hydroxyamino)(imino)methyl]-1H-indol-1-yl}propanoate (D96) (324mg, 1.05 mmol) and stirred at RT for 45 minutes. The solution was heated at 80 °C for 4 hours then left standing overnight. The solution was heated at 80 °C for a further 4 hours to give one major product. Evaporated off the DMF, added EtOAc (50ml) and washed with water (50ml). The EtOAc was washed with sat. aqueous sodium hydrogen carbonate (50ml) and water (50ml) then dried over MgSO₄.
- Evaporated off the solvent and crystallised from ethanol to yield the title compound as 280mg of cream solid. δ H (400 MHz, d₆-DMSO) 1.10 (3H, t), 2.90 (2H, t), 3.99-4.05 (5H, m), 4.49 (2H, t), 7.38 (1H, d), 7.74 (1H, s), 7.80 (1H, d), 7.97 (1H, d), 8.21-8.23 (2H, m), 8.36 (1H, d). MS (ES) C₂₂H₁₉⁸¹Br³⁵ClN₃O₄ requires 505; found 506 (MH⁺).

Description for D107

Ethyl 3-(3-chloro-5-{5-[6-(methyloxy)-3-biphenyl]-1,2,4-oxadiazol-3-yl}-1*H*-indol-1-yl)propanoate (D107)



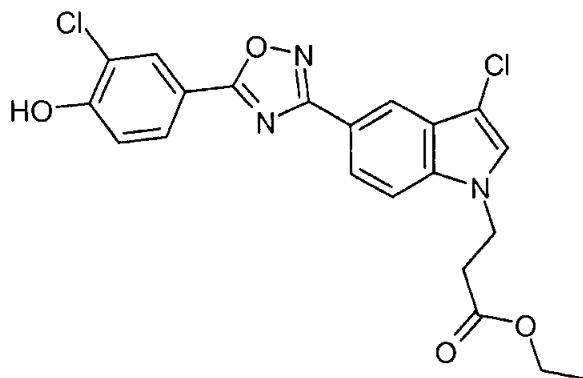
5

Ethyl 3-(5-{5-[3-bromo-4-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl}-3-chloro-1*H*-indol-1-yl)propanoate (**D106**) (212mg, 0.42 mmol), phenyl boronic acid (104mg, 0.84 mmol), Pd(PPh₃)₄ (20mg) and 2N aq. sodium carbonate solution (3ml, 6mmol) were suspended in DME (6ml) and heated at 90 °C for 2 hours. Added phenyl boronic acid (30mg, 0.24 mmol) and Pd(PPh₃)₄ (20mg) and heated at 90 °C for a further 2 hours. Added EtOAc (70ml) and washed with water (100ml). Dried over MgSO₄ and evaporated off the solvent. The residue was crystallised from ethanol to yield the title compound as 90mg of light tan solid. MS (ES) C₂₈H₂₄³⁵ClN₃O₄ requires 501; found 502 (MH⁺).

15

Description for D108

Ethyl 3-(3-chloro-5-[5-(3-chloro-4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]-1*H*-indol-1-yl)propanoate (D108)

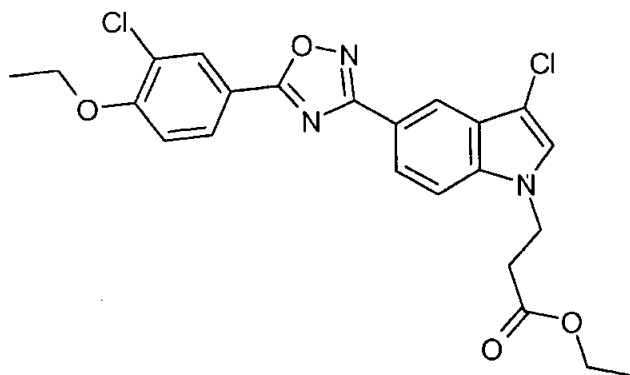


3-Chloro-4-hydroxybenzoic acid (commercial) (240mg, 1.40 mmol) in dry DMF (8ml) was treated with EDC (292mg, 1.52 mmol) and HOBt (208mg, 1.52 mmol) and stirred for 5 minutes. Added ethyl 3-{3-chloro-5-[(hydroxyamino)(imino)methyl]-1*H*-indol-1-yl}propanoate (**D96**) (432mg, 1.40 mmol) and stirred at RT for 30 minutes.

- 5 The reaction mixture was heated at 80 °C for 7 hours. Added EtOAc (70ml) and washed with water (70ml), sat. aq, sodium hydrogen carbonate (70ml) and water (70ml). Dried over MgSO₄ and evaporated off the solvent. The residue was subjected to chromatography using a biotage (EtOAc/hexane 1:2) to obtain the title compound as 200mg of white solid. δ H (400 MHz, d₆-DMSO) 1.10 (3H, t), 2.91 (2H, t), 4.04 (2H, q), 4.50 (2H, t), 7.67-7.70 (2H, m), 7.75 (1H, s), 7.80-7.81 (2H, m), 7.94 (1H, dd), 8.22-8.25 (1H, m), 10.95 (1H, broad s). MS (ES) C₂₁H₁₇³⁵Cl₂N₃O₄ requires 445; found 446 (MH⁺).
- 10

Description for D109

- 15 **Ethyl 3-(3-chloro-5-{5-[3-chloro-4-(ethoxy)phenyl]-1,2,4-oxadiazol-3-yl}-1*H*-indol-1-yl)propanoate (D109)**

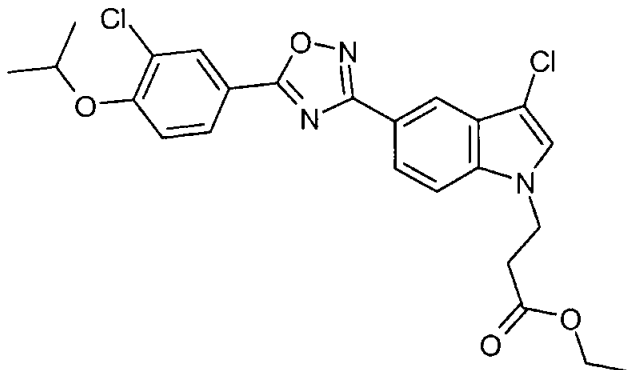


- 20 To ethyl 3-{3-chloro-5-[5-(3-chloro-4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]-1*H*-indol-1-yl}propanoate (**D108**) (180mg, 0.40 mmol) and K₂CO₃ (138mg, 1.0 mmol) in dry DMF (3ml) was added ethyl iodide (78mg, 0.50 mmol) and the mixture heated at 80 °C with stirring for 30 minutes. Cooled mixture and added EtOAc (50ml). Washed with water (3x40ml) and dried over MgSO₄. Evaporated off the solvent and crystallised
- 25 from ethanol to yield the title compound as 110mg of white solid. δ H (400 MHz, d₆-DMSO) 1.10 (3H, t), 1.42 (3H, t), 2.90 (2H, t), 4.02 (2H, q), 4.27 (2H, q), 4.49 (2H, t), 7.40 (1H, d), 7.74 (1H, s), 7.80 (1H, d), 7.95 (1H, dd), 8.16 (1H, dd), 8.21-8.22 (2H, m). MS (ES) C₂₃H₂₁³⁵Cl₂N₃O₄ requires 473; found 474 (MH⁺).

108

Description for D110

Ethyl 3-[3-chloro-5-(5-[3-chloro-4-[(1-methylethyl)oxy]phenyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoate (D110)



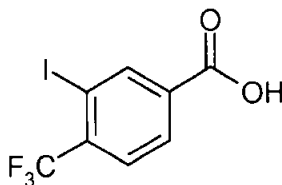
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To ethyl 3-{3-chloro-5-[5-(3-chloro-4-hydroxyphenyl)-1,2,4-oxadiazol-3-yl]-1H-indol-1-yl}propanoate (**D108**) (180mg, 0.40 mmol) and K_2CO_3 (138mg, 1.0 mmol) in dry DMF (5ml) was added isopropyl iodide (85mg, 0.50 mmol) and the mixture stirred at 80 °C for 30 minutes. Cooled mixture and added EtOAc (50ml). Washed with water (2X50ml) and dried over $MgSO_4$. Evaporated off the solvent and crystallised from ethanol to yield the title compound as 120 mg of white solid. δH (400 MHz, d_6 -DMSO) 1.12 (3H, t), 1.37 (6H, d), 2.91 (2H, t), 4.02 (2H, q), 4.50 (2H, t), 4.89-4.98 (1H, m), 7.72-7.85 (5H, m), 7.95-8.00 (1H, m), 8.24 (1H, d). MS (ES) $C_{24}H_{23}^{35}Cl_2N_3O_4$ requires 487; found 488 (MH^+).

15

Description for D111

3-Iodo-4-(trifluoromethyl)benzoic acid (D111)



3-Amino-4-(trifluoromethyl)benzoic acid (commercially available) (6.5 g, 31.7 mmol) and triiodomethane (37.4 g, 95.1 mmol) were dissolved in THF (300 ml). The reaction mixture was heated to 80 °C and then butyl nitrite (5.56 ml, 47.6 mmol) was added slowly at this temperature. Heating was continued at this temperature for 4 hours and then the reaction was concentrated *in vacuo* to give the crude product. Purification by column chromatography (hexane to 30% EtOAc in hexane). This

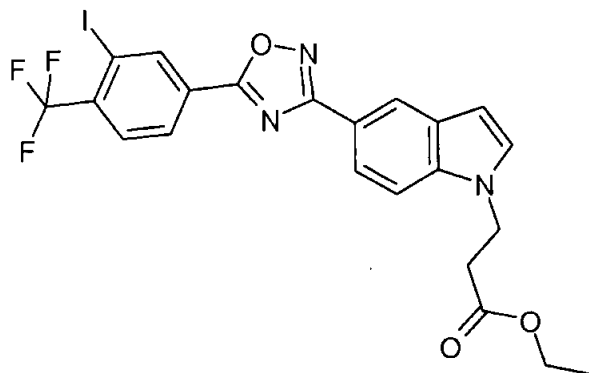
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material was combined with another batch from a similar reaction performed on 2 g of 3-amino-4-(trifluoromethyl)benzoic acid. The combined material was purified by preparative HPLC to give the title compound (6.1 g). MS $C_8H_4F_3IO_2$ requires 316; found 315 ($M-H^+$).

5

Description for D112

Ethyl 3-(5-{5-[3-iodo-4-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate (D112)



10 **D111** (1.0 g, 3.16 mmol) was dissolved in DMF (25 ml) under nitrogen. EDC (0.7 g, 3.7 mmol) and HOBt (0.5 g) were added. The reaction was stirred at room temperature for 15 minutes and then triethylamine (0.87 ml, 6.32 mmol) was added and the reaction was stirred for a further 5 minutes. **D52** (0.87 g, 3.16 mmol) was added and the reaction was stirred at room temperature overnight. The reaction was

15 concentrated *in vacuo* and the resultant oil diluted with ethyl acetate (100 ml). The organic layer was washed with water (2 x 30 ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product which was purified by column chromatography. The product was eluted in 7% EtOAc in hexane and evaporation afforded the title compound (0.45 g). MS $C_{22}H_{17}F_3IN_3O_3$ requires 555; found 556 (MH^+).

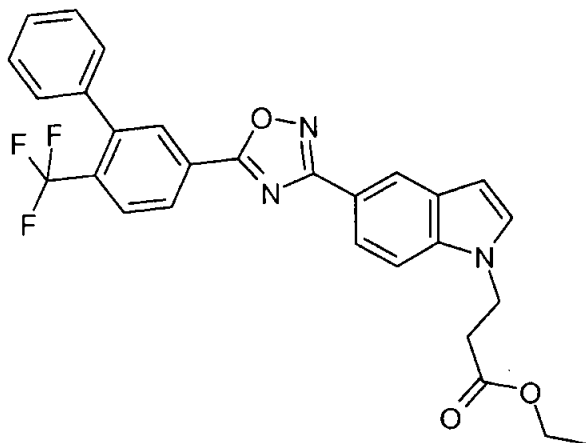
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110

Description for D113

Ethyl 3-(5-{5-[6-(trifluoromethyl)-3-biphenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate (D113)

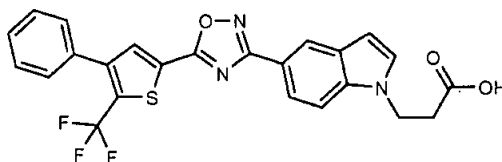


- 5 This material was prepared by a similar method to that used for **D107** from **D112**. MS (ES) $C_{28}H_{22}F_3N_3O_2$ requires 505; found 506 (MH^+).

Examples

10 **Example 1**

3-(5-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid (E1)

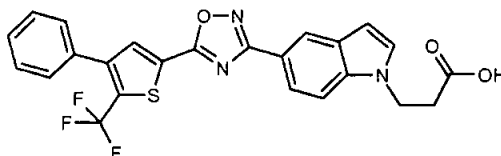


- D3** (38 mg) was dissolved in 2M aqueous NaOH (0.5 ml) and MeOH (0.5 ml) then stirred at RT overnight. LCMS analysis showed 41% product so the reaction mixture was heated to 50 °C and stirred over the weekend. LCMS showed the reaction to be complete. The reaction mixture was evaporated then partitioned between H_2O and DCM. The organic layer was extracted with H_2O . The combined aqueous extracts were acidified to pH = 1 and extracted with DCM. These DCM extracts were dried over $MgSO_4$, filtered and evaporated to give the crude product MF105672-149A1 (30 mg). The crude product was purified on a silica cartridge (12+S), eluting with a 0 to 10 % mixture of MeOH in DCM to give the purified product. This was dissolved in $CHCl_3$ and evaporated to give the title compound (3 mg) as a white solid. δH ($CDCl_3$,
- 15
- 20

400MHz): 2.92 (2H, t), 4.50 (2H, t), 6.51 (1H, d), 7.24 (1H, d), 7.40-7.53 (6H, m), 7.90 (1H, s), 8.00 (1H, d), 8.45 (1H, s). MS (ES⁺): C₂₄H₁₆F₃N₃O₃S requires 483; found 484 (MH⁺).

5 **Example 1 (alternative procedure)**

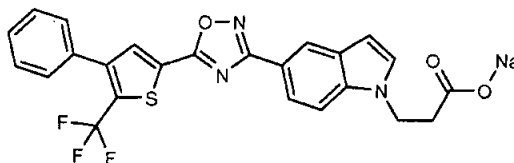
3-(5-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid (E1)



D3 (600 mg) was treated with 2 M aq. NaOH (25 ml) and MeOH (25 ml). This mixture was stirred overnight then heated to 50 °C for 6 hours. The MeOH was then evaporated and the remaining solution acidified and extracted with EtOAc (x 3). The combined organic solutions were washed with brine and evaporated to give the crude residue C(302 mg) as an off-white solid. This was triturated with cold MeOH to give the title compound (162 mg) as a grey solid. δ H (d₆-DMSO, 400MHz): 2.80 (2H, t), 4.46 (2H, t), 6.64 (1H, d), 7.49-7.59 (6H, m), 7.72 (1H, d), 7.85 (1H, dd), 8.22-8.25 (1H, m), 8.31-8.34 (1H, m). MS (ES): C₂₄H₁₆F₃N₃O₃S requires 483; found 484 (MH⁺).

Example 2

Sodium 3-(5-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propionate (E2)

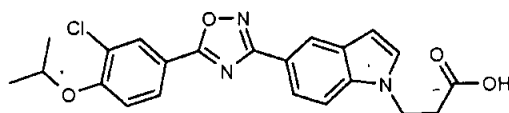


E1 (30 mg) was dissolved in EtOAc (1 ml), treated with 2M aqueous NaOH (40 μ l), diluted with H₂O (1 ml) and extracted with EtOAc (3 x 5 ml), using a small volume of brine during the third extraction to aid phase separation. The combined organics were evaporated to give the title compound (37 mg) as a green solid. δ H (methanol-d₄, 400MHz): 2.68 (2H, t), 4.48 (2H, t), 6.55 (1H, d), 7.49 (1H, d), 7.45-7.56 (5H, m), 7.62 (1H, d), 7.92 (1H, d), 8.03 (1H, s), 8.35 (1H, s). MS (ES⁺): C₂₄H₁₆F₃N₃O₃S requires 483; found 484 (MH⁺).

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Example 3

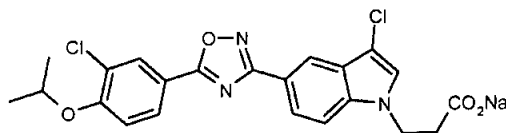
3-[5-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoic acid (E3)



- 5 **D6** MF105672-178A2 (38 mg) was dissolved in EtOH, treated with 12.5 M aqueous NaOH (2 ml) and stirred at RT for 4 hours. The reaction mixture was evaporated, re-dissolved in H₂O and washed with diethyl ether. The aqueous solution was acidified then extracted with DCM. The DCM solutions were combined, dried over MgSO₄, filtered and evaporated to give the title compound MF105672-181A1 (5 mg) as a pale yellow solid. δ H (CDCl₃, 400MHz): 1.44 (6H, d), 2.94 (2H, t), 4.51 (2H, t), 4.73 (1H, septet), 6.61 (1H, d), 7.07 (1H, d), 7.22 (1H, d), 7.45 (1H, d), 7.94 (1H, d), 8.07 (1H, d), 8.27 (1H, s), 8.47 (1H, s). MS (ES): C₂₂H₂₀ClN₃O₄ requires 425; found 426 (MH⁺).

Example 4

- 15 **Sodium** 3-[3-Chloro-5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoate (E4)

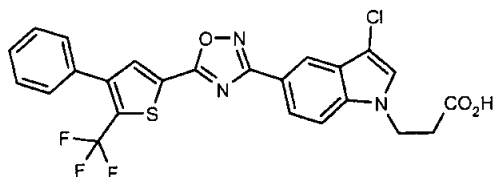


- D7** (200 mg) and Cs₂CO₃ (336 mg) were placed in a microwave vial, treated with DMF (2.8 ml) and ethyl 3-bromopropionate (99 μ l) and sonicated for 10 minutes. The mixture was then heated to 120 °C in a microwave reactor for 25 mins. The reaction mixture was then evaporated, re-dissolved in MeOH (10 ml) and treated with 2 M aq. NaOH (10 ml). This mixture was sonicated briefly and then heated to 50 °C overnight. The reaction mixture was then evaporated, diluted with H₂O (70 ml) and extracted with EtOAc, adding NaCl and acetone to improve the extraction. The organic extracts were evaporated to give the crude product which was acidified with HCl to give the free-acid. This was insufficiently soluble for purification by chromatography and so was triturated with MeOH, treated with 2M aq. NaOH (1.5 eq.), evaporated, dissolved in EtOAc, filtered and evaporated to give the title compound (56 mg) as a brown solid. δ H (methanol-d₄, 400MHz): 1.42 (6H, d), 2.66 (2H, t), 4.47 (2H, t), 4.82 (1H, m), 7.29 (1H, d), 7.44 (1H, s), 7.65 (1H, d), 7.98 (1H,

d), 8.12 (1H, d), 8.20 (1H, s), 8.30 (1H, s). MS (ES): $C_{22}H_{19}^{35}Cl_2N_3O_4$ requires 459; found 460 (MH^+).

Example 5

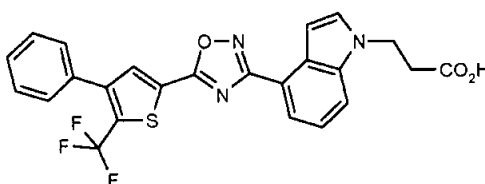
- 5 **3-(3-Chloro-5-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid (E5)**



- D8 (86 mg), 3-bromopropionate (52 mg), Cs_2CO_3 (126 mg) and DMF (1 ml) were placed in a microwave vial and stirred at 131 °C in the microwave reactor for 1.5 hours. The reaction mixture was then evaporated to dryness and treated with 2M aq. NaOH and EtOH (20 ml). This solution was stirred at 50 °C for 4 hours and then neutralised with HCl and evaporated to remove the EtOH. The aqueous solution was then extracted twice with EtOAc and the combined extracts evaporated. The residue was dissolved in DMSO, filtered, treated with MeCN causing precipitation of the product which was filtered and washed with MeCN to give the title compound (23 mg) as an off-white solid. δH (d_6 -DMSO, 400MHz): 2.47-2.57 (solvent + 2H) 4.37 (2H, t), 7.51-7.59 (5H, m), 7.72 (1H, s), 7.76 (1H, d), 7.89 (1H, d), 8.17 (1H, s), 8.25 (1H, s). MS (ES): $C_{24}H_{15}ClF_3N_3O_2S$ requires 517; found 516 ($M-H^+$).

Example 6

- 20 **3-(4-{5-[4-Phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid (E6)**



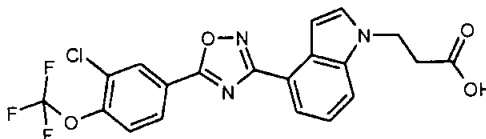
- D10 (85 mg, 0.207 mmol) was placed in a microwave vial with Cs_2CO_3 (135 mg) and DMF (1 ml). This was stirred briefly and ethyl bromopropionate (40 ul) was added. The mixture was heated at 130 °C for 1.5 hours in the microwave reactor. The reaction mixture was transferred to a flask containing 2 M aqueous NaOH (5 ml) and EtOH (5 ml), then stirred at room temperature overnight. The mixture was then evaporated and the residue acidified to pH = 2.5 with 2 M aqueous HCl. This solution

114
was extracted with EtOAc twice and the combined extracts evaporated to give a yellow residue which was purified by MDAP to give the title compound (50 mg) as a white solid. δ H (CDCl₃, 400MHz): 2.93 (2H, t), 4.50 (2H, t), 7.26 (1H, s), 7.33 (1H, d), 7.37 (1H, ap t), 7.45-7.52 (5H, m), 7.55 (1H, d), 7.93 (1H, s), 8.04 (1H, d). MS (ES):

5 C₂₄H₁₆F₃N₃O₃S requires 483; found 482 (M-H⁺).

Example 7

3-[4-(5-{3-Chloro-4-[(trifluoromethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoic acid (E7)



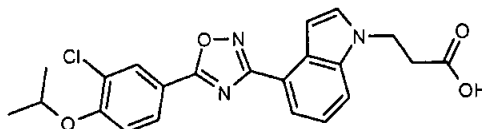
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3-Chloro-4-[(trifluoromethyl)oxy]benzoic acid (commercial source) (131 mg), EDCI (114 mg) and HOBT (81 mg) were dissolved in DMF (2.5 ml) and stirred at RT for 10 minutes. Ethyl 3-{5-[(hydroxyamino)(imino)methyl]-1H-indol-1-yl}propanoate (**D57**) (150 mg) in DMF (2.5 ml) was added and stirring continued at RT for 2 hours. The mixture was then heated at 80 °C overnight. The reaction mixture was evaporated to dryness then extracted with EtOAc (2 x 25 ml) from H₂O (25 ml). The combined organic solutions were evaporated to dryness and the residue treated with EtOH and 2 M aq. NaOH (1:1 mixture, 20 ml). This mixture was stirred at 50 °C for 2 hours then evaporated to remove the EtOH. The resultant precipitate was filtered off and washed with a mixture of H₂O and EtOH then 2 M HCl. The residue was recrystallised from hot EtOH to give the title compound (62 mg) as a white solid. δ H (d₆-DMSO, 400MHz): 2.81 (2H, t), 4.50 (2H, t), 7.08 (1H, d), 7.36 (1H, apparent t), 7.61 (1H, d), 7.83 (1H, d), 7.89 (1H, d), 7.96 (1H, d), 8.32 (1H, dd), 8.50 (1H, d). MS (ES⁻): C₂₀H₁₃³⁵ClF₃N₃O₄ requires 451; found 450 (M-H⁺).

25

Example 8

3-[4-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoic acid (E8)



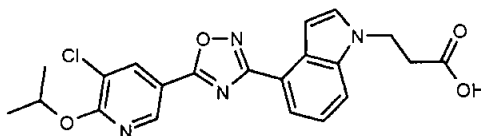
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3-chloro-4-[(1-methylethyl)oxy]benzoic acid (**D4**) (117 mg) was added to EDCI (114 mg) and HOBT (81 mg) dissolved in DMF (2.5 ml). This was stirred at RT for 10 minutes and then ethyl 3-[4-[(hydroxyamino)(imino)methyl]-1*H*-indol-1-yl]propanoate (**D57**) (150 mg) in DMF (2.5 ml) was added and stirring continued at RT for 2 hours then at 80 °C overnight. The reaction mixture was evaporated to dryness and extracted from H₂O (25 ml) with EtOAc (2 x 25 ml). The combined organics were evaporated and treated with 2 M aq. NaOH (10 ml) and EtOH (10 ml), stirred at 50 °C for 2 hours then evaporated to remove the EtOH. The remaining solution was acidified, filtered and the precipitate washed with EtO/H₂O then recrystallised from hot EtOH/H₂O then from DMSO. Washing with Et₂O and MeOH gave the title compound (46 mg) as a white solid. δ H (d_6 -DMSO, 400MHz): 1.37 (6H, d), 2.81 (2H, t), 4.50 (2H, t), 4.89 (1H, septet), 7.08 (1H, d), 7.35 (1H, apparent t), 7.46 (1H, d), 7.60 (1H, d), 7.81 (1H, d), 7.94 (1H, d), 8.15 (1H, dd), 8.23 (1H, d). MS (ES⁻): C₂₂H₂₀³⁵ClN₃O₄ requires 425; found 424 (M-H⁺).

15

Example 9

3-[4-(5-{5-Chloro-6-[(1-methylethyl)oxy]-3-pyridinyl)-1,2,4-oxadiazol-3-yl]-1*H*-indol-1-yl]propanoic acid (E9)



20 Ethyl 3-[4-[(hydroxyamino)(imino)methyl]-1*H*-indol-1-yl]propanoate (**D57**) (150 mg) in DMF (2.5 ml) was added to a solution of 5-chloro-6-[(1-methylethyl)oxy]-3-pyridinecarboxylic acid (**D61**) (118 mg), HOBT (81 mg) and EDCI (114 mg) which had been stirring at RT for 10 minutes in DMF (2.5 ml). The resultant mixture was stirred at RT for 2 hours then heated at 80 °C for three days. The reaction mixture was evaporated to dryness and extracted from H₂O (25 ml) with EtOAc (2 x 25 ml). The combined organics were evaporated and the residue stirred in EtOH/2 M aq. NaOH (1:1 mixture, 20 ml) at 50 °C for 2 hours. The EtOH was evaporated and the precipitate removed by filtration. This was acidified then purified by MDAP to give the title compound (48 mg) as an off white solid. δ H (d_6 -DMSO, 400MHz): 1.40 (6H, d), 2.80 (2H, t), 4.50 (2H, t), 5.46 (1H, septet), 7.08 (1H, d), 7.36 (1H, apparent t), 7.60 (1H, d), 7.82 (1H, d), 7.95 (1H, d), 8.60 (1H, d), 8.97 (1H, d). MS (ES⁻): C₂₁H₁₉³⁵ClN₄O₄ requires 426; found 425 (M-H⁺).

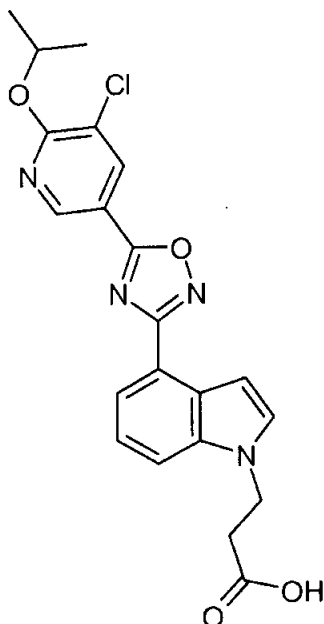
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Example 9 (alternative procedure)

3-[4-(5-{5-Chloro-6-[(1-methylethyl)oxy]-3-pyridinyl)-1,2,4-oxadiazol-3-yl]-1H-indol-1-yl]propanoic acid (E9)

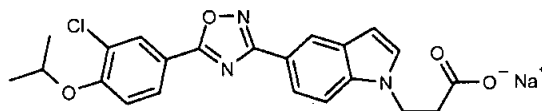


- 5 Ethyl 3-[4-(5-{5-chloro-6-[(1-methylethyl)oxy]-3-pyridinyl)-1,2,4-oxadiazol-3-yl]-1H-indol-1-yl]propanoate (**D62**) (1.1 g, 2.418 mmol) was dissolved in a mixture of 1,4-dioxane (100 ml) and ethanol (100 ml). Water (50.0 ml) was added followed by 2N sodium hydroxide (2.418 ml, 4.84 mmol). The mixture was stirred at RT for one and a half hours to give a single product. Evaporated off most of the solvent, acidified with
- 10 glacial acetic acid, added water (50ml) and extracted product into EtOAc (200ml). Washed with water (30ml) and dried over MgSO_4 . The solvent was evaporated off until a white precipitate was formed. The solid was filtered off and washed with ether. Mass of title compound obtained was 780mg. δH (400 MHz, d_6 -DMSO) 1.38 (6H, d), 2.81 (2H, t), 4.50 (2H, t), 5.41-5.51 (1H, m), 7.07 (1H, dd), 7.36 (1H, t), 7.59 (1H, d),
- 15 7.81 (1H, d), 7.94 (1H, dd), 8.58 (1H, d), 8.96 (1H, d), 12.40 (1H, broad s). MS (ES) $\text{C}_{21}\text{H}_{19}^{35}\text{ClN}_4\text{O}_4$ requires 426; found 427 (MH^+).

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Example 10

Sodium 3-[5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoate (E10)



5

(D5) (200 mg) was dissolved in DMF (4 ml), treated with Cs_2CO_3 (368 mg) and then ethylbromopropionate (109 μl). The resultant mixture was heated to 120 °C in a microwave reactor for 2 hours. The reaction mixture was decanted from the insoluble residue and evaporated to dryness to give a pale orange oil

- 10 This oil was dissolved in EtOH (2 ml) and treated with 2 M aqueous NaOH (2 ml). This produced a white precipitate so a further portion of EtOH (2 ml) was added to produce a homogeneous solution. The resultant mixture was heated to 60 °C for 1 hour then stood at RT overnight. The reaction mixture was evaporated to dryness, re-dissolved in H_2O (10 ml), treated with brine (2 ml) and extracted with a mixture of
- 15 EtOAc and MeCN (2 x 20 ml). Evaporation gave the crude product (313 mg) as a pale green solid. This was dissolved in MeOH (5 ml), filtered and evaporated then triturated with Et_2O to give the title compound (247 mg) as a pale green solid. δH (methanol- d_4 , 400MHz): 1.42 (6H, d), 2.68 (2H, t), 4.48 (2H, t), 4.83 (1H, septet), 6.55 (1H, dd), 7.30 (1H, d), 7.38 (1H, d), 7.61 (1H, d), 7.91 (1H, dd), 8.12 (1H, dd),
- 20 8.21 (1H, d), 8.34 (1H, dd). MS (ES^+): $\text{C}_{22}\text{H}_{20}\text{ClN}_3\text{O}_4$ requires 425 found 424 ($\text{M}-\text{H}^+$).

The following compounds were prepared in an similar manner to example 1. The solvent for the hydrolysis step was either methanol or ethanol and the reaction temperature between room temperature and 60 °C. In some cases the reactions

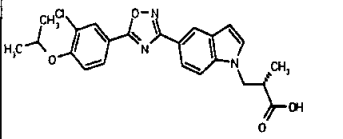
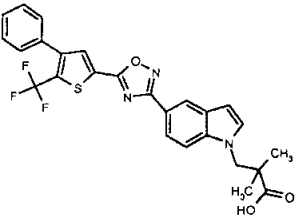
25 were worked up by extracting the product or acidified product into an organic solvent and in other cases the final compound precipitated from the aqueous layer and was isolated by filtration. Purification was by MDAP, trituration or recrystallisation.

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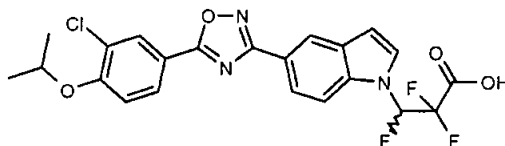
Example	Structure	Name	Comments	MS
E11		(5-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)acetic acid	Hydrolysis of D42	470 (MH ⁺)
E12		sodium 3-[3-bromo-5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoate	Hydrolysis of D43	504 (M-H ⁺ for ³⁵ Cl & ⁸¹ Br)
E13		sodium 5-[5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]pentanoate	Hydrolysis of D44	454 (MH ⁺ for ³⁵ Cl)
E14		4-[5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]butanoic acid	Hydrolysis of D45	440 (MH ⁺ for ³⁵ Cl)
E15		(2R)-3-[5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]-2-methylpropanoic acid	Hydrolysis of D46	440 (MH ⁺ for ³⁵ Cl)

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E16		(2S)-3-[5-(5-(3-chloro-4-[(1-methylethyl)oxy]phenyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]-2-methylpropanoic acid	Hydrolysis of D47	440 (MH ⁺ for ³⁵ Cl)
E17		2,2-dimethyl-3-(5-(5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl)propanoic acid	Hydrolysis of D48.	512 (MH ⁺)

Example 18

3-[5-(5-(3-Chloro-4-[(1-methylethyl)oxy]phenyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]-2,2,3-trifluoropropanoic acid (E18)



5

D5 (200 mg), Cs₂CO₃ (552 mg) and DMF (2.8 ml) were stirred at RT and treated with 3-bromo-2,2,3-trifluoropropanoic acid (175 mg). This mixture was heated at 140 °C for 1 hour in a microwave reactor. 2 further equivalents of Cs₂CO₃ (368 mg) were added and heating continued at 140 °C for 10 hours. The reaction mixture was then

10 evaporated, treated with H₂O, shaken and filtered to give a brown solid residue. This was purified by MDAP to give the title compound (12 mg) as a white solid. δ H (methanol-d₄, 400MHz): 1.42 (6H, d), 4.83 (1H, septet), 6.87 (1H, d), 7.29 (1H, d), 7.45 (1H, d), 7.54 (1H, d), 7.61 (1H, d), 7.80 (1H, d), 8.06 (1H, d), 8.11 (1H, d), 8.19-8.22 (1H, m), 8.44 (1H, s).

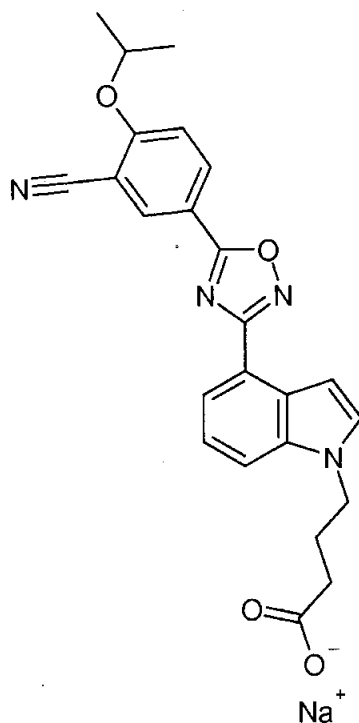
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Example 19

Sodium 4-[4-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]butanoate (E19)

5



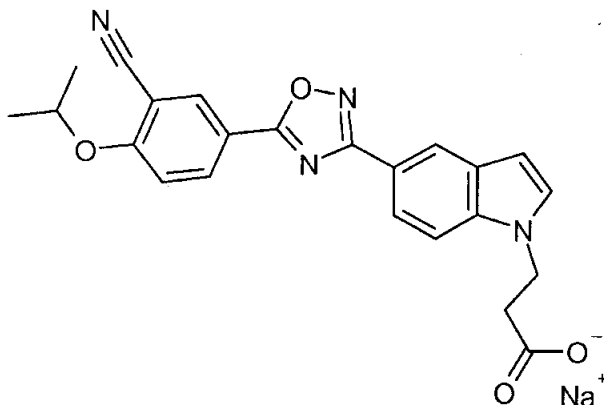
To a solution of ethyl 4-[4-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]butanoate (**D65**) (1.42g, 3.09 mmol) in a mixture of dioxan (70ml) and ethanol (70ml) was treated with 2N sodium hydroxide (1.86ml, 3.71 mmol) followed by water (35ml). The solution was stirred at RT for 4 hours. Evaporated off most of the solvent and filtered off the white solid from the remaining solvent. Washed the solid with water followed by ether and dried to give 580mg of the title compound. δ H (400 MHz, methanol- d_4) 1.45 (6H, d), 2.09-2.22 (4H, m), 4.30 (2H, t), 4.92-4.98 (1H, m), 7.15 (1H, d), 7.31 (1H, t), 7.38-7.43 (2H, m), 7.69 (1H, d), 7.95 (1H, d), 8.43-8.46 (2H, m). MS (ES) $C_{24}H_{22}N_4O_4$ requires 430; found 431 (MH^+).

20

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Example 20

Sodium 3-[5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoate



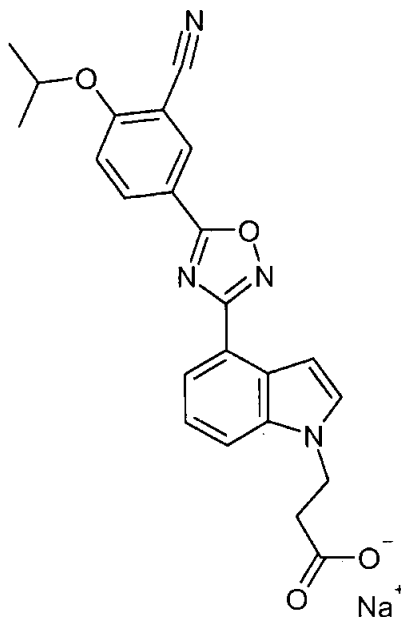
5 Ethyl 3-[5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoate (**D53**) (150mg, 0.38 mmol) was dissolved in ethanol (25ml) by warming to 60 °C. Allowed solution to cool to RT then added 2N sodium hydroxide (3ml, 6 mmol). The solution was stirred at RT for 30 minutes. LC/MS showed a single
10 product. Evaporated off the ethanol and filtered off the solid which precipitated out of solution. Mass of title compound as a light tan solid obtained on drying was 50mg. δ H (400 MHz, d_6 -DMSO) 1.45 (6H, d), 2.67 (2H, t), 4.48 (2H, t), 4.92-4.98 (1H, m), 6.54-6.55 (1H, m), 7.34 (1H, d), 7.38 (1H, d), 7.60 (1H, d), 7.91 (1H, dd), 8.35 (1H, d), 8.41-8.46 (2H, m). MS (ES) $C_{23}H_{20}N_4O_4$ requires 416; found 417 (MH^+).

15

Example 21

Sodium 3-[4-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoate (**E21**)

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Ethyl 3-[4-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoate (**D63**) (81mg, 0.18 mmol) was dissolved in ethanol by warming to 50 °C. Added 2N sodium hydroxide (0.25ml, 0.5 mmol) followed by water (2ml), warmed to 50 °C to give a clear solution then left standing at RT for 30 minutes. LC/MS showed a single product. The ethanol was evaporated off to obtain a precipitate which was filtered off and dried. Mass of title compound as a pale brown solid obtained was 60 mg δ H (400 MHz, d_6 -DMSO) 1.39 (6H, d), 2.32 (2H, t), 4.39 (2H, t), 4.96-5.00 (1H, m), 7.01 (1H, d), 7.31 (1H, t), 7.56-7.61 (2H, m), 7.74 (1H, d), 7.91 (1H, d), 8.45 (1H, dd), 8.55 (1H, d). MS (ES) $C_{23}H_{20}N_4O_4$ requires 416; found 417 (MH⁺).

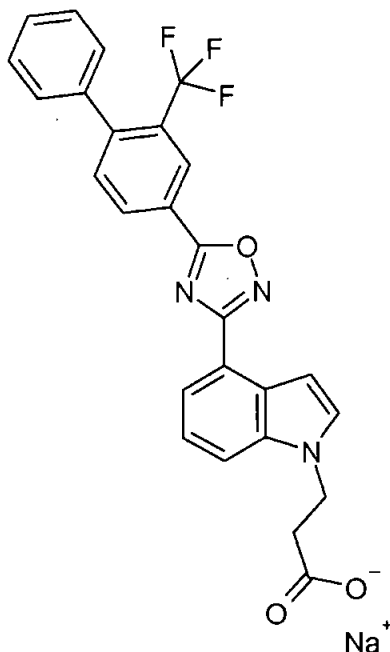
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Example 22

Sodium 3-(4-{5-[2-(trifluoromethyl)-4-biphenyl]-1,2,4-oxadiazol-3-yl}-1*H*-indol-1-yl)propanoate (E22)



5 Ethyl 3-(4-{5-[2-(trifluoromethyl)-4-biphenyl]-1,2,4-oxadiazol-3-yl}-1*H*-indol-1-yl)propanoate (**D64**) (15mg, 0.31 mmol) was dissolved in ethanol (50ml) by warming to 40 °C for 10 minutes then 2N sodium hydroxide (4ml, 8 mmol) was added followed by water (8ml). The solution was left standing for 1 hour. Evaporated off the ethanol and filtered off the off-white solid. Mass of title compound as a beige
 10 obtained on drying was 42 mg. δ H (400 MHz, methanol- d_4) 2.69 (2H, t), 4.53 (2H, t), 7.17-7.18 (1H, m), 7.32-7.40 (3H, m), 7.46-4.49 (4H, m), 7.66 (1H, d), 7.75 (1H, d), 8.02 (1H, d), 8.53 (1H, dd), 8.63 (1H, d). MS (ES) $C_{26}H_{18}F_3N_3O_3$ requires 477; found 478 (MH^+).

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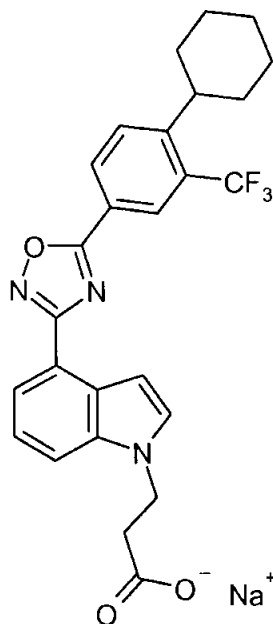
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Example 23

Sodium 3-(4-{5-[4-cyclohexyl-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate (E23)

5



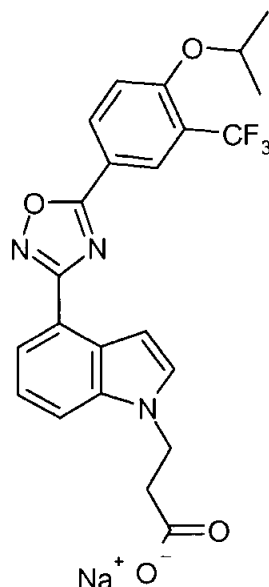
Ethyl 3-(4-{5-[4-cyclohexyl-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate (**D69**) (63 mg, 0.123 mmol) was dissolved in ethanol (8 ml) and sodium hydroxide (2M, 0.5 ml, 1.000 mmol) was added. The reaction was heated at 40 °C for 18 h. LCMS showed complete conversion to product. The reaction mixture was concentrated *in vacuo* and the white solid filtered off and washed with water. On filtration, much compound redissolved and passed through, so solid and filtrate were combined and separated between dichloromethane (10 mL) and 2M HCl (3 mL). The aqueous phase was extracted with further dichloromethane (10 mL). The organic phases were isolated by phase separator, combined and the solvent removed *in vacuo*. The solid was then dissolved in acetonitrile and water with addition of an equimolar amount of sodium hydroxide (2M, 53 µL) before the solution was freeze-dried to give the title compound (42 mg) as a white solid. δ H (methanol- d_4 , 400 MHz): 8.48 (1H, d), 8.43 (1H, dd), 7.98 (1H, dd), 7.86 (1H, d), 7.73 (1H, d), 7.46 (1H, d), 7.32 (1H, app. t), 7.15 (1H, dd), 4.52 (2H, t), 3.04 (1H, t), 2.69 (2H, t),

125

2.0-1.8 (5H, m), 1.63 (2H, dd), 1.53-1.37 (3H, m). MS (ES) $C_{26}H_{24}F_3N_3O_3$ requires 483; found 482 ($M-H^+$).

Example 24

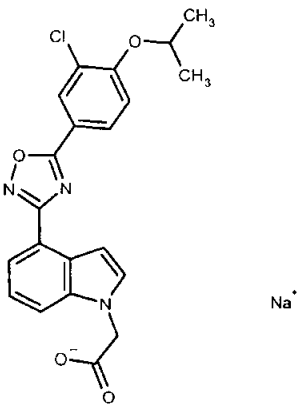
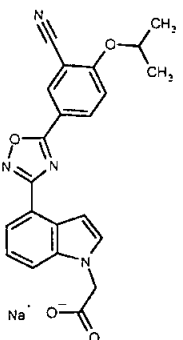
- 5 Sodium 3-(4-{5-[4-[(1-methylethyl)oxy]-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1*H*-indol-1-yl)propanoate (E24)



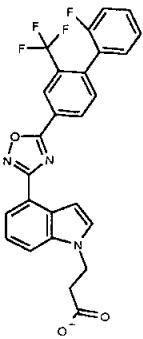
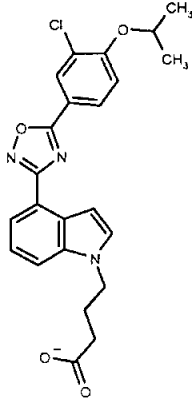
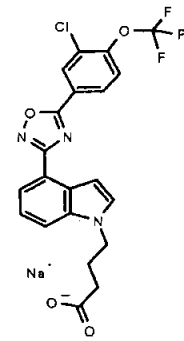
- To a suspension of ethyl 3-(4-{5-[4-[(1-methylethyl)oxy]-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1*H*-indol-1-yl)propanoate (**D72**) (81 mg, 0.17 mmol) in ethanol (8mL) was added aqueous sodium hydroxide (2M, 0.8 mL, 1.6 mmol) and the reaction heated to 50 °C to dissolve the reagents before heating at 40 °C for 1 h. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate (20 mL) and water (20 mL) and acidified with aqueous hydrochloric acid (2M). The aqueous phase was extracted with further ethyl acetate (2 x 20 mL) and the combined organic extracts dried (phase separator) and concentrated *in vacuo*. The solid was then dissolved in acetonitrile and water with addition of an equimolar amount of sodium hydroxide (2M) before the solution was freeze-dried to give the title compound (57 mg). δ H (d_6 -DMSO, 400 MHz): 8.44 (1H, dd), 8.35 (1H, d), 7.93 (1H, dd), 7.74 (1H, d), 7.65-7.54 (2H, m), 7.31 (1H, app. t), 7.00 (1H, dd) 4.99 (1H, septet), 4.38 (2H, t), 2.34 (2H, t), 1.36 (6H, d). MS (ES): $C_{23}H_{20}F_3N_3O_4$ requires 459; found 460 (MH^+).

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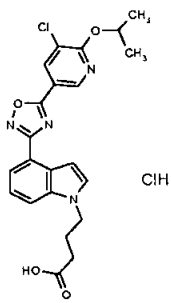
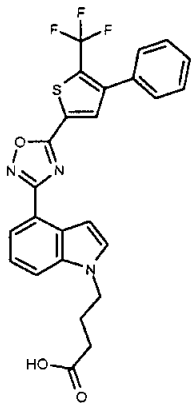
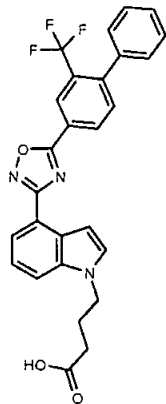
The following examples were prepared by similar hydrolysis reactions to those described above. At least two equivalents of sodium hydroxide were used. The solvent was either ethanol or methanol. In some cases a cosolvent (dichloromethane or dioxane) was used to aid dissolution of the starting material. The reactions were carried out at a temperature between room temperature and 50 °C. In some cases the some or all of the solvent was removed after the reaction was complete. The reactions were either worked up by partitioning between an organic and an aqueous layer or by filtering the solid product from the aqueous solvent. In some cases the crude products were purified by trituration. Products were either isolated as the acid or the sodium salt.

	Structure	precursor	Name	MS
E25	 Na ⁺	D73	sodium [4-(5-(3-chloro-4-[(1-methylethyl)oxy]phenyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]acetate	412 (MH ⁺ for ³⁵ Cl)
E26	 Na ⁺	D74	sodium [4-(5-(3-cyano-4-[(1-methylethyl)oxy]phenyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]acetate	403 (MH ⁺)

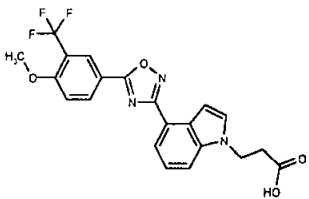
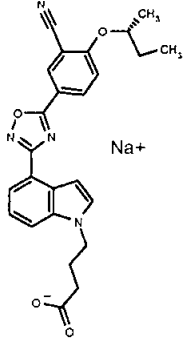
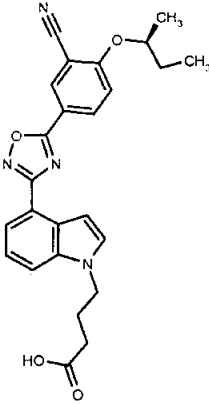
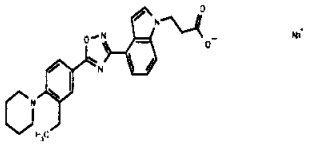
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E27	 Na ⁺	D76	sodium 3-(4-(5-(2'-fluoro-2-(trifluoromethyl)-4-biphenyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl)propanoate	496 (MH ⁺)
E28	 Na ⁺	D77	sodium 4-[4-(5-(3-chloro-4-((1-methylethyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]butanoate	440 (MH ⁺ for ³⁵ Cl)
E29	 Na ⁺	D78	sodium 4-[4-(5-(3-chloro-4-((trifluoromethyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]butanoate	466 (MH ⁺ for ³⁵ Cl)

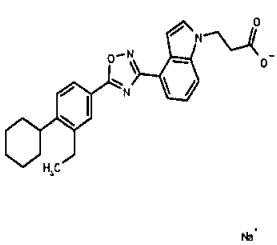
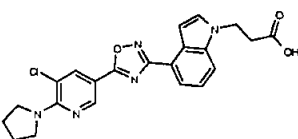
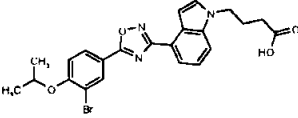
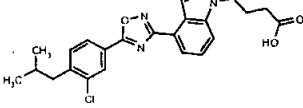
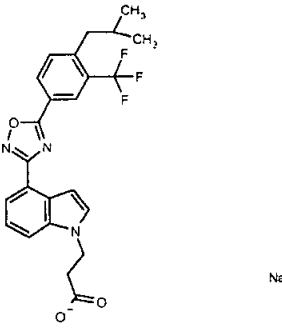
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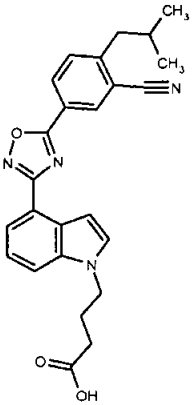
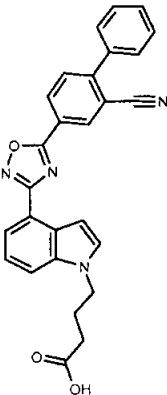
E30		D79	4-[4-(5-(5-chloro-6-[(1-methylethyl)oxy]-3-pyridinyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]butanoic acid hydrochloride	441 (MH ⁺ for ³⁵ Cl)
E31		D80	4-(4-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)butanoic acid	498 (MH ⁺)
E32		D81	4-(4-{5-[2-(trifluoromethyl)-4-biphenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)butanoic acid	492 (MH ⁺)

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E33		D82	3-(4-{5-[4-(methoxy)-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid	432 (MH ⁺)
E34		D83	sodium 4-{4-[5-(3-cyano-4-[(1R)-1-methylpropyl]oxy)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl}butanoate	445 (MH ⁺)
E35		D84	4-{4-[5-(3-cyano-4-[(1S)-1-methylpropyl]oxy)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl}butanoic acid	445 (MH ⁺)
E36		D85	sodium 3-(4-{5-[3-ethyl-4-(1-piperidinyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate	445 (MH ⁺)

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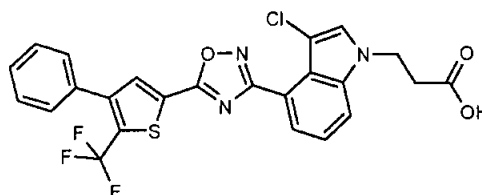
E37		D86	sodium 3-(4-{5-(4-cyclohexyl-3-ethylphenyl)-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate	444 (MH ⁺)
E38		D87	3-(4-{5-[5-chloro-6-(1-pyrrolidinyl)-3-pyridinyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid	438 (MH ⁺ for ³⁵ Cl)
E39		D88	4-[4-{5-[3-bromo-4-[(1-methylethyl)oxy]phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl]butanoic acid	484 (MH ⁺ for ⁷⁹ Br)
E40		D89	4-(4-{5-[3-chloro-4-(2-methylpropyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)butanoic acid	438 (MH ⁺ for ³⁵ Cl)
E41		D90	sodium 3-(4-{5-[4-(2-methylpropyl)-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate	456 (M-H ⁺)

E42		D91	4-(4-{5-[3-cyano-4-(2-methylpropyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)butanoic acid	429 (MH ⁺)
E43		D92	4-(4-{5-[2-cyano-4-biphenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)butanoic acid	447 (M-H ⁺)

Example 44

3-(3-Chloro-4-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-

5 1H-indol-1-yl)propanoic acid (E44)

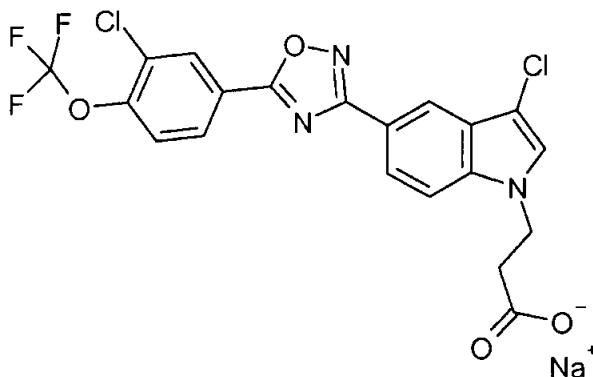


This material was prepared in a similar fashion to **E5** (from **D93**) except that the alkylation step took 4.5 h in the microwave and the hydrolysis step was carried out at room temperature overnight. MS (ES): C₂₄H₁₅ClF₃N₃O₃S requires 517; found 516 (M-H⁺).

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Example 45

Sodium 3-[3-chloro-5-(5-{3-chloro-4-[(trifluoromethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoate (E45)



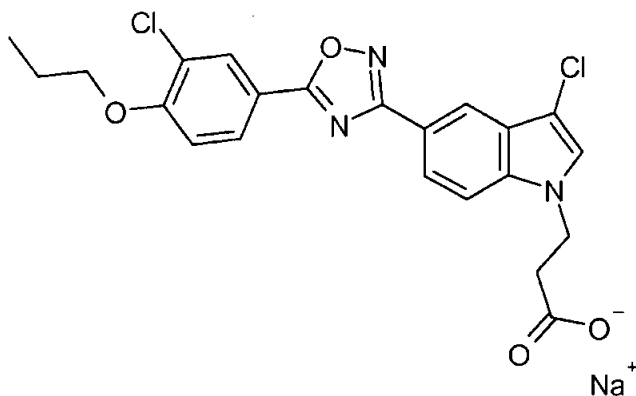
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To ethyl 3-[3-chloro-5-(5-{3-chloro-4-[(trifluoromethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoate (**D97**) (150mg, 2.9 mmol) in ethanol (10ml) was added 2N NaOH (2ml, 4 mmol) and the mixture heated at 50 °C for 30 minutes. Evaporated off the ethanol and filtered off the pale cream solid which had precipitated out of the remaining solution. Mass of title compound obtained on drying was 100mg. ^1H (400 MHz, d_6 -DMSO) 2.35 (2H, t), 4.35 (2H, t), 7.73-7.75 (2H, m), 7.86 (1H, d), 7.92 (1H, d), 8.22 (1H, s), 8.30-8.32 (1H, m), 8.49 (1H, d). MS (ES) $\text{C}_{20}\text{H}_{12}^{35}\text{Cl}_2\text{F}_3\text{N}_3\text{O}_4$ requires 485; found 486 (MH^+)

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Example 46

Sodium 3-(3-chloro-5-{5-[3-chloro-4-(propyloxy)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate (E46)

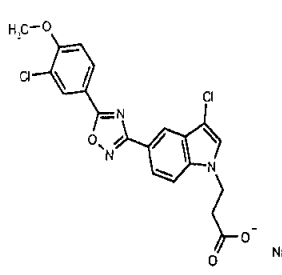


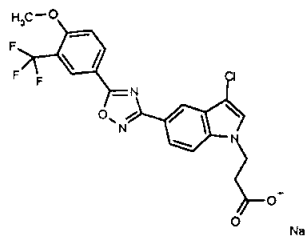
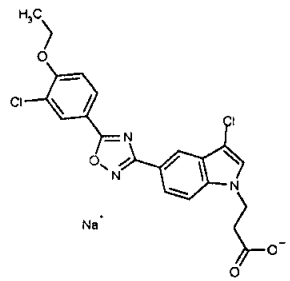
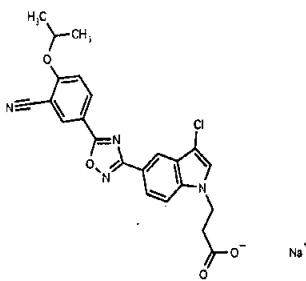
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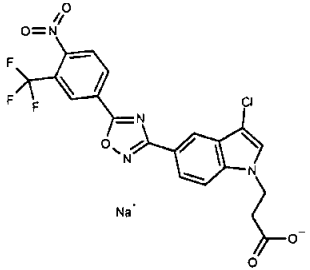
To ethyl 3-(3-chloro-5-{5-[3-chloro-4-(propyloxy)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate (**D101**) (120mg, 2.5 mmol) in ethanol (10ml) was added 2N NaOH (2ml) and the mixture heated at 50 °C for 30 minutes. Evaporated off the ethanol and filtered off the white solid which had precipitated out of the remaining solution. Mass of title compound obtained on drying was 85mg. δ H (400 MHz, d_6 -DMSO) 1.03 (3H, t), 1.77-1.86 (2H, m), 2.34 (2H, t), 4.17 (2H, t), 4.35 (2H,t), 7.40 (1H,d), 7.71-7.74 (2H,m), 7.91 (1H, d), 8.15 (1H,dd), 8.20-8.21 (2H,m). MS (ES) $C_{22}H_{19}^{35}Cl_2N_3O_4$ requires 459; found 460 (MH^+).

10 The following examples were prepared by a similar method to those described above, using 2-60 equivalents of sodium hydroxide (Table 8). The reactions were worked up by removing the ethanol and filtering the resultant solid or extracting the product into ethyl acetate. If required the products were purified by trituration with ether.

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	Structure	precursor	Name	MS
E47		D102	sodium 3-(3-chloro-5-{5-[3-chloro-4-(methoxy)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate	430, 432 (M- H^+ for $^{35}Cl_2$, $^{35}Cl^{37}Cl$)

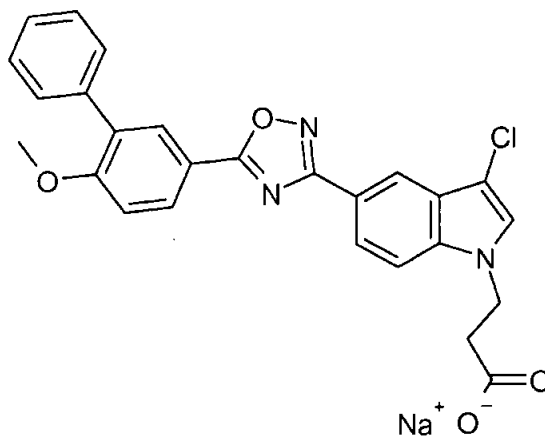
E48		D103	sodium 3-(3-chloro-5-{5-[4-(methoxy)-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate	466 (MH ⁺ for ³⁵ Cl)
E49		D109	sodium 3-(3-chloro-5-{5-[3-chloro-4-(ethoxy)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate	444, 446 (M-H ⁺ for ³⁵ Cl ₂ , ³⁵ Cl ³⁷ Cl)
E50		D104	sodium 3-[3-chloro-5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoate	451 (MH ⁺ for ³⁵ Cl)

E51		D105	sodium 3-(3-chloro-5-{5-[4-nitro-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate	478, 480 in ES ⁺
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Example 53

Sodium 3-(3-chloro-5-{5-[6-(methyloxy)-3-biphenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate (E53)

5



10 Ethyl 3-(3-chloro-5-{5-[6-(methyloxy)-3-biphenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoate (**D107**) (90mg, 0.18 mmol) was heated in ethanol (10ml) to give a clear solution. This solution was treated with 2N sodium hydroxide (3ml, 6 mmol) and stirred at 50 °C for 30 minutes. Evaporated off the ethanol and filtered off the white solid that precipitated out of solution, washing the solid with a small amount of water and ether. Stirred solid in a small amount of acetone for 1 hour, filtered, washed with a small amount of ether and dried to yield the title compound as 45mg of white solid.

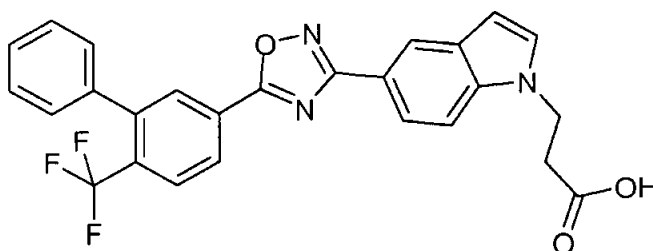
15 δ H (400 MHz, d_6 -DMSO) 2.34 (2H, t), 3.91 (3H, s), 4.34 (2H, t), 7.41-7.46 (2H, m),

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7.48-7.50 (2H, m), 7.57-7.59 (2H, m), 7.63-7.66 (2H, m), 7.80 (1H, d), 8.10 (1H, d), 8.10-8.25 (2H, m). MS (ES) $C_{26}H_{20}^{35}ClN_3O_4$ requires 473; found 474 (MH^+).

Example 54

- 5 3-(5-{5-[6-(Trifluoromethyl)-3-biphenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid (E54)



- This material was prepared by a similar method to prepare **E53**. The solvent was a mixture of ethanol and 1,4-dioxane and 0.071 ml of 2M aq. NaOH was used to hydrolyse 51 mg of **D113**. MS (ES) $C_{26}H_{18}F_3N_3O_3$ requires 477; found 476 ($M-H^+$).
- 10

GTP γ S binding assay

- Rat basophilic eukaemia cells (RBL) stably expressing S1P1 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 homogenised in 20 volumes assay buffer (20mM HEPES pH 7.4, 100mM NaCl, 10mM $MgCl_2 \cdot 6H_2O$, 10 μ M GDP Saponin 10 μ g/ml). The membrane suspension was further centrifuged for 20 minutes at 20,000rpm re-homogenised and spun again. Following the second centrifugation the pellet was re-suspended in an appropriate volume (1ml for each flask of cells) and assayed for protein concentration.
- 15
- 20

- Concentrated stock of S1P was sonicated before serial dilutions were prepared from a starting concentration of 10^{-5} M. Diluted membranes (10 μ g/well) were incubated with various concentrations of S1P and 0.3nM ^{35}S -GTP γ S (NEN; specific activity 1250 Ci/mmol) in 96 deep well plates. Binding was performed at 30°C for 45 minutes and terminated by harvesting the membranes onto GF/B filter plates using a Packard Universal Harvester. After drying the plates for 45 minutes, 50 μ l of Microscint 0 was added to each well and binding measured on a Topcount NXT (Perkin Elmer). Data was analysed using Graphpad Prism 4 and expressed as
- 25
- 30

percentage stimulation above basal. EC50 values were defined as the concentration of agonist required to give 50% of the maximal stimulation.

Membrane preparation (alternative method)

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

S1P1 GTPγS assay (alternative method)

- 20 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, MgCl₂ 10mM, NaCl 100mM and pH adjusted to 7.4 using KOH 5M, GDP 10µM FAC (final assay concentration) and saponin 90µg/ml
25 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 [³⁵S]-GTPγS (0.5nM final radioligand conc) made up in assay buffer was then added to agonist plates. The final assay cocktail (10.1µl)
30 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
35 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.

Exemplified compounds of the invention that were tested in this assay had a pEC50
5 > 5.

S1P3

S1P3 membranes from rat basophilic leukaemia cells (RBL-2H3)(1.5µg/well) were adhered to WGA-coated SPA beads (0.125mg/well) in assay buffer (HEPES 20mM,
10 MgCl₂ 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 [³⁵S]-GTPγS (0.5nM final radioligand conc) made up
15 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
20 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.

25 Exemplified compounds tested in this assay had a pEC50 < 6, many had a pEC50 <5.

Yeast assay

Yeast (*Saccharomyces cerevisiae*) cells expressing the human S1P1 receptor were generated by integration of an expression cassette into the *ura3* chromosomal locus of yeast strain MMY23. This cassette consisted of DNA sequence encoding the human S1P1 receptor flanked by the yeast GPD promoter to the 5' end of S1P1 and
35 a yeast transcriptional terminator sequence to the 3' end of S1P1. MMY23 expresses a yeast/mammalian chimeric G-protein alpha subunit in which the C-terminal 5 amino acids of Gpa1 are replaced with the C-terminal 5 amino acids of human Gαi1/2 (as described in Brown *et al.* (2000), *Yeast* 16:11-22). Cells were grown at 30°C in liquid

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Synthetic Complete (SC) yeast media (Guthrie and Fink (1991), Methods in Enzymology, Vol. 194) lacking uracil, tryptophan, adenine and leucine to late logarithmic phase (approximately 6 OD₆₀₀/ml).

Agonists were prepared as 10 mM solutions in DMSO. EC₅₀ values (the concentration required to produce 50% maximal response) were estimated using 4 fold dilutions (BiomekFX, Beckman) into DMSO. Agonist solutions in DMSO (1% final assay volume) were transferred into black microtitre plates from Greiner (384-well). Cells were suspended at a density of 0.2 OD₆₀₀/ml in SC media lacking histidine, uracil, tryptophan, adenine and leucine and supplemented with 0.1mM 3-aminotriazole, 0.1M sodium phosphate pH 7.0, and 10μM fluorescein di-β-D-glucopyranoside (FDGlu). This mixture (50ul per well) was added to agonist in the assay plates (Multidrop 384, Labsystems). After incubation at 30°C for 24 hours, fluorescence resulting from degradation of FDGlu to fluorescein due to exoglucanase, an endogenous yeast enzyme produced during agonist-stimulated cell growth, was determined using a fluorescence microtitre plate reader (Tecan Spectrofluor or LJJ Analyst excitation wavelength: 485nm; emission wavelength: 535nm). Fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter fit to generate a concentration effect value. Efficacy (E_{max}) was calculated from the equation

$$E_{\max} = \frac{\text{Max}_{[\text{compound X}]} - \text{Min}_{[\text{compound X}]}}{\text{Max}_{[\text{S1P}]} - \text{Min}_{[\text{S1P}]}} \times 100\%$$

where Max_[compound X] and Min_[compound X] are the fitted maximum and minimum respectively from the concentration effect curve for compound X, and Max_[S1P] and Min_[S1P] are the fitted maximum and minimum respectively from the concentration effect curve for Sphingosine-1-Phosphate (available from Sigma). Equieffective molar ratio (EMR) values were calculated from the equation

$$\text{EMR} = \text{EC}_{50 [\text{compound X}]} / \text{EC}_{50 [\text{S1P}]}$$

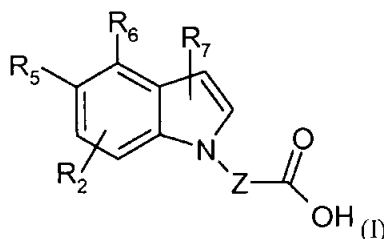
Where EC_{50 [compound X]} is the EC₅₀ of compound X and EC_{50 [S1P]} is the EC₅₀ of S1P.

Where tested, exemplified compounds of the invention had a pEC₅₀ > 4.5 in the yeast assay.

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Claims

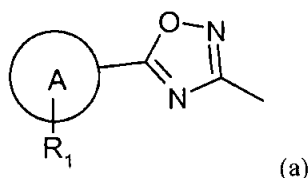
- 5 1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



wherein

one of R_5 and R_6 is hydrogen or R_2 and the other is (a)

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

R_1 is hydrogen or up to three substituents independently selected from halogen, $C_{(1-6)}$ alkyl, $C_{(3-6)}$ cycloalkyl, $C_{(1-6)}$ alkoxy, $C_{(3-6)}$ cycloalkyloxy, trifluoromethoxy, difluoromethoxy, trifluoromethyl, cyano, nitro, optionally substituted piperidine, optionally substituted pyrrolidine, optionally substituted phenyl and optionally substituted 5 or 6 membered heteroaryl rings;

when R_1 is phenyl, piperidine, pyrrolidine or a 5 or 6 membered heteroaryl ring it may be substituted by up to three substituents selected from halogen, $C_{(1-6)}$ alkyl, $C_{(1-6)}$ alkoxy, trifluoromethoxy, difluoromethoxy, $C_{(3-6)}$ cycloalkyl, trifluoromethyl and cyano;

R_2 is hydrogen or up to three substituents independently selected from halogen, $C_{(1-4)}$ alkyl, $C_{(1-4)}$ alkoxy, trifluoromethoxy, difluoromethoxy, trifluoromethyl and cyano;

R_7 is hydrogen or halogen;

Z is $C_{(1-4)}$ alkyl which is optionally interrupted by N or O and is optionally substituted by halogen or methyl.

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2. A compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein:
- R₅ is hydrogen and R₆ is (a); and/or
- A is thienyl, pyridyl or phenyl; and/or
- 5 R₁ is up to three substituents selected from halogen, C₁₋₆alkoxy, or trifluoromethyl, optionally substituted phenyl, optionally substituted cyclohexyl, cyano, trifluoromethoxy, optionally substituted piperidine, optionally substituted pyrrolidine, C₁₋₆alkyl and NO₂; and/or
- R₂ is hydrogen; and/or
- 10 R₇ is hydrogen or halogen; and/or
- Z is C₍₁₋₄₎alkyl which is optionally interrupted by N or O and is optionally substituted by fluoro or methyl.

3. A compound selected from:

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3-(5-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1*H*-indol-1-yl)propanoic acid

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

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

30

3-(3-Chloro-5-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1*H*-indol-1-yl)propanoic acid

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3-(4-{5-[4-Phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1*H*-indol-1-yl)propanoic acid

3-[4-(5-{3-Chloro-4-[(trifluoromethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]propanoic acid

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

- 3-[4-(5-{5-Chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]propanoic acid
- 5 3-[5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]propanoic acid
- (5-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1*H*-indol-1-yl)acetic acid
- 10 3-[3-bromo-5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]propanoic acid
- 5-[5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]pentanoic acid
- 15 4-[5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]butanoic acid
- 4-[5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]butanoic acid
- 20 (2*S*)-3-[5-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]-2-methylpropanoic acid
- 25 2,2-dimethyl-3-(5-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1*H*-indol-1-yl)propanoic acid
- 3-[5-(5-{3-Chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]-2,2,3-trifluoropropanoic acid
- 30 4-[4-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]butanoic acid
- 3-[5-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1*H*-indol-1-yl]propanoic acid
- 35

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- 3-[4-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoic acid
- 3-(4-{5-[2-(trifluoromethyl)-4-biphenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid
- 5 3-(4-{5-[4-cyclohexyl-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid
- 10 3-(4-{5-[4-[(1-methylethyl)oxy]-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid
- 15 4-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]acetic acid
- 4-(5-{3-cyano-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]acetic acid
- 20 3-(4-{5-[2'-fluoro-2-(trifluoromethyl)-4-biphenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid
- 4-[4-(5-{3-chloro-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]butanoic acid
- 25 4-[4-(5-{3-chloro-4-[(trifluoromethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]butanoic acid
- 30 4-[4-(5-{5-chloro-6-[(1-methylethyl)oxy]-3-pyridinyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]butanoic acid
- 4-(4-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)butanoic acid
- 35 4-(4-{5-[2-(trifluoromethyl)-4-biphenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)butanoic acid
- 3-(4-{5-[4-(methyloxy)-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid
- 40 4-{4-[5-(3-cyano-4-[(1R)-1-methylpropyl]oxy)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl]butanoic acid

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- 4-{4-[5-(3-cyano-4-[(1S)-1-methylpropyl]oxy)phenyl]-1,2,4-oxadiazol-3-yl]-1H-indol-1-yl}butanoic acid
- 5 3-(4-{5-[3-ethyl-4-(1-piperidinyl)phenyl]-1,2,4-oxadiazol-3-yl]-1H-indol-1-yl)propanoic acid
- 3-(4-[5-(4-cyclohexyl-3-ethylphenyl)-1,2,4-oxadiazol-3-yl]-1H-indol-1-yl)propanoic acid
- 10 3-(4-{5-[5-chloro-6-(1-pyrrolidinyl)-3-pyridinyl]-1,2,4-oxadiazol-3-yl]-1H-indol-1-yl)propanoic acid
- 4-[4-(5-{3-bromo-4-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]butanoic acid
- 15 4-(4-{5-[3-chloro-4-(2-methylpropyl)phenyl]-1,2,4-oxadiazol-3-yl]-1H-indol-1-yl)butanoic acid
- 20 3-(4-{5-[4-(2-methylpropyl)-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl]-1H-indol-1-yl)propanoic acid
- 4-(4-{5-[3-cyano-4-(2-methylpropyl)phenyl]-1,2,4-oxadiazol-3-yl]-1H-indol-1-yl)butanoic acid
- 25 4-{4-[5-(2-cyano-4-biphenyl)-1,2,4-oxadiazol-3-yl]-1H-indol-1-yl}butanoic acid
- 3-(3-Chloro-4-{5-[4-phenyl-5-(trifluoromethyl)-2-thienyl]-1,2,4-oxadiazol-3-yl]-1H-indol-1-yl)propanoic acid
- 30 3-[3-chloro-5-(5-{3-chloro-4-[(trifluoromethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoic acid
- 35 3-(3-chloro-5-{5-[3-chloro-4-(propyloxy)phenyl]-1,2,4-oxadiazol-3-yl]-1H-indol-1-yl)propanoic acid
- 3-(3-chloro-5-{5-[3-chloro-4-(methyloxy)phenyl]-1,2,4-oxadiazol-3-yl]-1H-indol-1-yl)propanoic acid

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3-(3-chloro-5-{5-[4-(methyloxy)-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid

- 5 3-(3-chloro-5-{5-[3-chloro-4-(ethyloxy)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid

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

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3-(3-chloro-5-{5-[4-nitro-3-(trifluoromethyl)phenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid

- 15 3-[3-chloro-5-(5-{4-chloro-3-[(1-methylethyl)oxy]phenyl}-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl]propanoic acid

3-(3-chloro-5-{5-[6-(methyloxy)-3-biphenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid

- 20 3-(5-{5-[6-(trifluoromethyl)-3-biphenyl]-1,2,4-oxadiazol-3-yl}-1H-indol-1-yl)propanoic acid

and pharmaceutically acceptable salts thereof.

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

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

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6. Use according to claim 4, wherein the condition is multiple sclerosis.

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

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

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9. Use according to claim 7, wherein the condition is multiple sclerosis.

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

11. A method of treatment for conditions or disorders in mammals including humans which can be mediated via the S1P1 receptors.

20

12. A method of treatment according to claim 11, wherein the condition is multiple sclerosis.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/064185

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D413/04 C07D413/14 A61K31/405 A61P37/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) 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, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 2007/116866 A (ASTELLAS PHARMA INC [JP]; HARADA HIRONORI [JP]; HATTORI KAZUYUKI [JP];) 18 October 2007 (2007-10-18) cited in the application page 49; compounds 47-4, 47-9, 47-10, 47-12	1-12
P, A	JP 2007 262009 A (DAIICHI SEIYAKU CO) 11 October 2007 (2007-10-11) the whole document	1-12
A	WO 2004/103279 A (MERCK & CO INC [US]; COLANDREA VINCENT J [US]; DOHERTY GEORGE A [US];) 2 December 2004 (2004-12-02) page 5, line 15 - page 8, line 9 page 39, line 1 - page 39, line 10 -/--	1-12
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents: * A* document defining the general state of the art which is not considered to be of particular relevance * E* earlier document but published on or after the international filing date * L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) * O* document referring to an oral disclosure, use, exhibition or other means * P* document published prior to the international filing date but later than the priority date claimed * T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention * X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone * Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. * &* document member of the same patent family		
Date of the actual completion of the international search 18 April 2008		Date of mailing of the international search report 25/04/2008
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Uselli, Ambrogio

1209

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2007/064185

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/032465 A (MERCK & CO INC [US]; DOHERTY GEORGE A [US]; HALE JEFFREY J [US]; LEGIE) 14 April 2005 (2005-04-14) page 5, line 11 - page 6, line 24 page 13, line 30 - page 14, line 6 -----	1-12

250

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/064185

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

Although claims 4-6,11,12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 8.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2007/064185

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2007116866	A	18-10-2007	NONE	
JP 2007262009	A	11-10-2007	NONE	
WO 2004103279	A	02-12-2004	AU 2004240586 A1 CA 2524867 A1 CN 1788008 A EP 1625123 A2 JP 2006528980 T	02-12-2004 02-12-2004 14-06-2006 15-02-2006 28-12-2006
WO 2005032465	A	14-04-2005	AU 2004277947 A1 CA 2539438 A1 CN 1859908 A EP 1670463 A2 JP 2007528872 T US 2007043014 A1	14-04-2005 14-04-2005 08-11-2006 21-06-2006 18-10-2007 22-02-2007

52

DERIVADOS INDOL COMO AGONISTAS DEL RECEPTOR S1P1

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

El 1-fosfato de esfingosina (S1P) es un mediador lípido bioactivo formado por la fosforilación de esfingosina mediante esfingosina cinasas y se encuentra en altos niveles en la sangre. Es producido y seretado por diversos tipos de células, incluidas las de origen hematopoyético tales como plaquetas y mastocitos (Okamoto et al 1998 J Biol Chem 273(42):27104; Sanchez y Hla 2004, J Cell Biochem 92:913). Tiene un amplio espectro de acciones biológicas, incluida la regulación de la 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 sensible 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 receptores de los genes de diferenciación endotelial acoplados a la proteína G (Chun et al 2002 Pharmacological Reviews 54:265, Sanchez y Hla 2004 J Cellular Biochemistry, 92:913). Estos 5 receptores presentan expresión de ARNm diferencial, estando S1P1-3 ampliamente expresado, S1P4 expresado en tejidos linfoides y hematopoyéticos y S1P5 principalmente expresado en el cerebro y en menor grado en el bazo. Señalizan mediante diferentes subgrupos de proteínas G para estimular una gama 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 el receptor S1P1 incluyen el tráfico de linfocitos, la inducción/supresión de citocinas y los efectos sobre las células endoteliales (Rosen y Goetzl 2005 Nat Rev Immunol. 5:560). Los agonistas del receptor S1P1 se han usado en diversos modelos de autoinmunidad y trasplante en animales, incluyendo los modelos de encefalomiелitis autoinmunitaria experimental (EAE) de MS, para disminuir la gravedad de la enfermedad inducida (Brinkman et al 2003 JBC 277:21453; Fujino et al 2003 J Pharmacol Exp Ther 305:70; Webb et al 2004 J Neuroimmunol 153:108; Rausch et al 2004 J Magn Reson Imaging 20:16). Se describe que esta inmunidad está mediada por el efecto de los agonistas de S1P1 sobre la circulación de linfocitos a través del sistema linfático. El tratamiento con agonistas de S1P1 da como resultado el secuestro de linfocitos dentro de órganos

B

linfoides secundarios tales como los ganglios linfáticos, induciendo 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). Los datos publicados sobre agonistas sugieren que el tratamiento con el
5 compuesto induce la pérdida del receptor S1P1 de la superficie celular mediante 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 disminución del receptor S1P1 sobre las células del sistema inmunitario lo que contribuye a la disminución del retroceso de las células T desde los ganglios linfáticos hasta el torrente sanguíneo.

10

La supresión del gen S1P1 causa letalidad embrionaria. Los experimentos para examinar el papel del receptor S1P1 en la migración y el tráfico de linfocitos han incluido la transferencia adoptiva de células T deficientes en S1P1 marcadas en los ratones de tipo salvaje irradiados. Estas células mostraron menos egresión desde
15 órganos linfoides secundarios (Matloubian et al 2004 Nature 427:355).

También se ha atribuido a S1P1 un papel en la modulación de la unión a las células endoteliales (Allende et al 2003 102:3665, Blood Singelton et al 2005 FASEB J 19:1646). Con respecto a esta acción endotelial, se ha descrito que los agonistas de
20 S1P1 tienen un efecto sobre los ganglios linfáticos aislados que pueden estar contribuyendo a un papel en la modulación de los trastornos del sistema inmunitario. Los agonistas de S1P1 causaron un cierre de las "puertas" del estroma endotelial de los senos linfáticos que drenan los ganglios linfáticos y evitan la egresión de los linfocitos (Wei et al 2005, Nat. Immunology 6:1228).

25

Se ha demostrado que el compuesto inmunosupresor FTY720 (JP11080026-A) disminuye los linfocitos circulantes en animales y el hombre, tienen actividad moduladora de enfermedades en modelos animales de trastornos inmunitarios y disminuyen las velocidades de remisión en esclerosis múltiple de recaída y remisión
30 (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
35 2006 New Eng J Medicine 335:1124). Este compuesto es un profármaco que es fosforilado in vivo por esfingosina quinasas para dar una molécula que tiene

actividad agonista en los receptores S1P1, S1P3, S1P4 y S1P5. Los estudios clínicos han demostrado que el tratamiento con FTY720 da como resultado bradicardia en las primeras 24 horas de tratamiento (Kappos et al 2006 New Eng J Medicine 335:1124). Se cree que la bradicardia es debida a agonismo en el receptor

5 S1P3, en base a cierto número de experimentos con animales y basados en células. Entre ellos, se incluye el uso de animales genosuprimidos que, a diferencia de los ratones naturales, no demuestran bradicardia tras la administración de FTY720 y el uso de compuestos selectivos para S1P1. (Hale et al 2004 Bioorganic & Medicinal Chemistry Letters 14:3501, Sanna et al 2004 JBC 279:13839, Koyrakh et al 2005

10 American J Transplantation 5:529)

Por esto, existe necesidad de compuestos agonistas del receptor S1P1 con selectividad sobre S1P3 que pueda esperarse que presenten una tendencia reducida a inducir bradicardia.

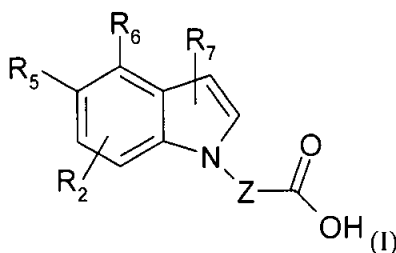
15 Las siguientes solicitudes de patentes describen derivados de oxadiazol como agonistas de S1P1: WO03/105771, WO05/058848, WO06/047195, WO06/100633, WO06/115188, WO06/131336, WO07/024922 y WO07/116866.

20 La siguiente solicitud de patente describe derivados de indol-oxadiazol como agentes antipicornavirales: WO96/009822. Las siguientes solicitudes de patentes describen derivados de ácidos indolcarboxílicos como antagonistas de receptores leucotriénicos, plaguicidas y fungicidas agroquímicos, respectivamente: WO06/090817, EP 0 439 785 y DE 39 39 238.

25 Ahora se ha encontrado una clase estructuralmente nueva de compuestos que proporciona agonistas del receptor S1P1.

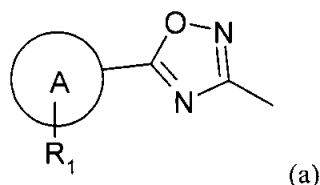
Por lo tanto, la presente invención proporciona compuesto de fórmula (I) o una sal

30 farmacéuticamente aceptable del mismo:



en la que

uno de R_5 y R_6 es hidrógeno o R_2 y el otro es (a)



A es un fenilo o un anillo heteroarílico de 5 o 6 miembros;

5 R_1 es hidrógeno o hasta tres sustituyentes independientemente seleccionados de halógeno, alquilo $C_{(1-6)}$, cicloalquilo $C_{(3-6)}$, alcoxi $C_{(1-6)}$, cicloalquilo $C_{(3-6)}$, trifluorometoxi, difluorometoxi, trifluorometilo, ciano, nitro, piperidina opcionalmente sustituida, pirrolidina opcionalmente sustituida, fenilo opcionalmente sustituido y anillos heteroarílicos de 5 o 6 miembros opcionalmente sustituidos;

10 cuando R_1 es fenilo, piperidina, pirrolidina o un anillo heteroarílico de 5 o 6 miembros puede estar sustituido con hasta tres sustituyentes seleccionados de halógeno, alquilo $C_{(1-6)}$, alcoxi $C_{(1-6)}$, trifluorometoxi, difluorometoxi, cicloalquilo C_{3-6} , trifluorometilo y ciano;

R_2 es hidrógeno o hasta tres sustituyentes independientemente seleccionados de halógeno, alquilo $C_{(1-4)}$, alcoxi $C_{(1-4)}$, trifluorometoxi, difluorometoxi, trifluorometilo y ciano;

R_7 es hidrógeno o halógeno;

Z es alquilo $C_{(1-4)}$ que está opcionalmente interrumpido con N o O y está opcionalmente sustituido con halógeno o metilo.

20

En una realización, cuando A es fenilo o piridilo R_1 es dos sustituyentes en las posiciones para y meta en A respecto del anillo de oxadiazol.

25 En una realización, Cuando A es tienilo R_1 es dos sustituyentes en las posiciones 4 y 5.

En una realización de la invención,

R_5 es hidrógeno y R_6 es (a); y/o

A es tienilo, piridilo o fenilo; y/o

30 R_1 es hasta tres sustituyentes seleccionados de halógeno, alcoxi C_{1-6} , o trifluorometilo, fenilo opcionalmente sustituido, ciclohexilo opcionalmente sustituido, ciano, trifluorometoxi, piperidina opcionalmente sustituida, pirrolidina opcionalmente sustituida, alquilo C_{1-6} y NO_2 ; y/o

R₂ es hidrógeno; y/o

R₇ es hidrógeno o halógeno; y/o

Z es alquilo C₍₁₋₄₎ que está opcionalmente interrumpido con N o O y está opcionalmente sustituido con fluoro o metilo.

5

En una realización de la invención,

R₅ es hidrógeno y R₆ es (a); y/o

A es piridilo o fenilo; y/o

10 R₁ es hasta dos sustituyentes seleccionados de halógeno, alcoxi C₁₋₆, o trifluorometilo, fenilo opcionalmente sustituido, ciclohexilo opcionalmente sustituido; ciano, trifluorometoxi, piperidina opcionalmente sustituida, pirrolidina opcionalmente sustituida, alquilo C₁₋₆ y NO₂; y/o

R₂ es hidrógeno; y/o

R₇ es hidrógeno, cloro o bromo; y/o

15 Z es alquilo C₍₂₋₃₎ no sustituido.

En una realización de la invención,

R₅ es hidrógeno y R₆ es (a); y/o

A es piridilo o fenilo; y/o

20 R₁ es hasta dos sustituyentes seleccionados de cloro, bromo, metoxi, propoxi, isopropoxi, trifluorometilo, fenilo sustituido con halo, fenilo, ciclohexilo, ciano, trifluorometoxi, piperidina, pirrolidina, etilo o NO₂; y/o

R₂ es hidrógeno; y/o

R₇ es hidrógeno, cloro o bromo; y/o

25 Z es alquilo C₍₂₋₃₎ no sustituido.

En una realización de la invención,

R₅ es hidrógeno y R₆ es (a); y/o

A es piridilo o fenilo; y/o

30 R₁ es hasta dos sustituyentes seleccionados de cloro, isopropoxi y ciano; y/o

R₂ es hidrógeno; y/o

R₇ es hidrógeno; y/o

Z es alquilo C₍₂₋₃₎ no sustituido.

35 En una realización de la invención,

R₅ es (a) y R₆ es hidrógeno.

A es tiofeno o fenilo opcionalmente sustituido; y/o

R₁ es hidrógeno, halógeno, alcoxi C₁₋₄, o trifluorometilo; y/o

R₂ es hidrógeno; y/o

Z es etileno.

5

En otra realización de la invención,

R₅ es (a) y R₆ es hidrógeno; y/o

A es tiofeno sustituido con fenilo; y/o

R₁ es hidrógeno, halógeno, alcoxi C₁₋₄, o trifluorometilo; y/o

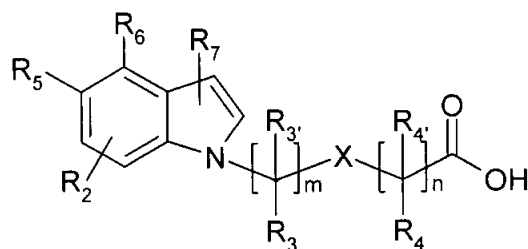
10 R₂ es hidrógeno; y/o

Z es etileno.

cuando R₁ es fenilo o un anillo heteroarílico de 5 ó 6 miembros puede estar sustituido con hasta tres sustituyentes seleccionados de halógeno, alquilo C₍₁₋₄₎,

15 alcoxi C₍₁₋₄₎, trifluorometoxi, difluorometoxi, trifluorometilo y ciano;

Por lo tanto, la presente invención también proporciona compuestos de fórmula (I) o una de sus sales farmacéuticamente aceptables:

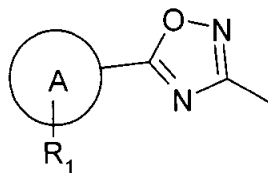


20

(IA)

donde:

uno de R₅ y R₆ es hidrógeno o R₂ y el otro es (a)



25

(a)

A es un fenilo o un anillo heteroarílico de 5 o 6 miembros;

- R_1 es hidrógeno o hasta tres sustituyentes independientemente seleccionados de halógeno, alquilo $C_{(1-4)}$, alcoxi $C_{(1-4)}$, trifluorometoxi, difluorometoxi, trifluorometilo, ciano, fenilo opcionalmente sustituido y anillos heteroarílicos de 5 ó 6 miembros opcionalmente sustituidos;
- 5 R_2 es hidrógeno o hasta tres sustituyentes independientemente seleccionados de halógeno, alquilo $C_{(1-4)}$, alcoxi $C_{(1-4)}$, trifluorometoxi, difluorometoxi, trifluorometilo y ciano;
- cada uno de R_3 , R_3' , R_4 y R_4' se seleccionan independientemente de hidrógeno, halógeno y metilo;
- 10 R_7 es hidrógeno o halógeno;
- X es NH opcionalmente sustituido con metilo, O, CH_2 opcionalmente sustituido con fluoro o metilo, o un enlace directo;
- m es 0-2; y
- n es 0-4.
- 15 cuando R_1 es fenilo o un anillo heteroarílico de 5 ó 6 miembros puede estar sustituido con hasta tres sustituyentes seleccionados de halógeno, alquilo $C_{(1-4)}$, alcoxi $C_{(1-4)}$, trifluorometoxi, difluorometoxi, trifluorometilo y ciano;
- 20 Cuando X es NH puede estar sustituido con metilo.
- Cuando X es CH_2 puede estar sustituido con fluoro o metilo.
- En una realización de la invención,
- A es tiofeno o fenilo opcionalmente sustituido;
- 25 R_1 es hidrógeno, halógeno, alcoxi C_{1-4} , o trifluorometilo;
- cada uno de R_2 , R_3 y R_4 es hidrógeno;
- X es un enlace directo;
- m es 2; y
- n es 0.
- 30 En otra realización de la invención,
- A es tiofeno sustituido con fenilo;
- R_1 es hidrógeno, halógeno, alcoxi C_{1-4} , o trifluorometilo;
- cada uno de R_2 , R_3 y R_4 es hidrógeno;
- 35 X es un enlace directo;
- m es 2; y

n es 0

El término "alquilo" como grupo o parte de un grupo, p.ej. alcoxi o hidroxialquilo se refiere a un grupo alquilo lineal o ramificado en todas las formas isómeras. El
5 término "alquilo $C_{(1-6)}$ " se refiere a un grupo alquilo, como se ha definido antes, que contiene al menos 1, y a lo sumo 6 átomos de carbono. Ejemplos de estos grupos alquilo incluyen metilo, etilo, propilo, *iso*-propilo, *n*-butilo, *iso*-butilo, *sec*-butilo, o *terc*-butilo. Ejemplos de tales grupos alcoxi incluyen metoxi, etoxi, *n*-propoxi, *iso*-propoxi, *n*-butoxi, *iso*-butoxi, *sec*-butoxi y *terc*-butoxi.

10

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

Los grupos cicloalquiloxi $C_{(3-6)}$ adecuados incluyen ciclopropoxi, ciclobutoxi,
15 ciclopentoxi y ciclohexiloxi.

Tal 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).

20

El término "heteroarilo" representa un anillo insaturado que comprende uno o más heteroátomos. Cuando el término heteroarilo representa un grupo de 5 miembros, contiene un heteroátomo seleccionado entre O, N o S y opcionalmente puede
25 contener de 1 a 3 átomos de nitrógeno adicionales. Cuando el heteroarilo representa un grupo de 6 miembros, contiene de 1 a 3 átomos de nitrógeno. Los ejemplos de tales anillos heteroarílicos de 5 o 6 miembros incluyen pirrolilo, triazolilo, tiadiazolilo, tetrazolilo, imidazolilo, pirazolilo, isotiazolilo, tiazolilo, isoxazolilo, oxazolilo, oxadiazolilo, furazanilo, furanilo, tienilo, piridilo, pirimidinilo, pirazinilo, piridazinilo y triazinilo.

30

En algunos de los compuestos de fórmula (I), dependiendo de la naturaleza del sustituyente hay átomos de carbono quirales y, por lo tanto, los compuestos de
fórmula (I) pueden existir como estereoisómeros. La invención se extiende a todos los isómeros ópticos tales como los estereoisómeros de los compuestos de fórmula
35 (I) incluyendo los enantiómeros, diastereoisómeros y las mezclas de los mismos, tales como los racematos. Las diferentes formas estereoisómeras pueden

separarse o resolverse entre sí mediante métodos convencionales, o cualquier isómero dado puede obtenerse mediante síntesis estereoselectivas o asimétricas convencionales.

- 5 Algunos de los compuestos de la presente invención pueden existir en diversas formas tautómeras y hay que entender que la invención abarca todas estas formas tautómeras.

Los compuestos preferidos de la invención son:

10

Ácido 3-(5-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1*H*-indol-1-il)propanoico

Ácido 3-[5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1*H*-indol-1-

15

il]propanoico

Ácido 3-[3-cloro-5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1*H*-indol-1-il]propanoico

20

Ácido 3-(3-cloro-5-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1*H*-indol-1-il)propanoico

Ácido 3-(4-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1*H*-indol-1-il)propanoico

25

Ácido 3-[4-(5-{3-cloro-4-[(trifluorometil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1*H*-indol-1-il]propanoico

Ácido 3-[4-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1*H*-indol-1-

30

il]propanoico

Ácido 3-[4-(5-{5-cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-1*H*-indol-1-il]propanoico

35

Ácido 3-[5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1*H*-indol-1-il]propanoico

- Ácido (5-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)acético
- 5 Ácido 3-[3-bromo-5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoico
- Ácido 5-[5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]pentanoico
- 10 Ácido 4-[5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoico
- Ácido 4-[5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoico
- 15 Ácido (2S)-3-[5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]-2-metilpropanoico
- Ácido 2,2-dimetil-3-(5-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- 20 Ácido 3-[5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]-2,2,3-trifluoropropanoico
- 25 Ácido 4-[4-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoico
- Ácido 3-[5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoico
- 30 Ácido 3-[4-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoico
- Ácido 3-(4-{5-[2-(trifluorometil)-4-biphenilil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- 35

Ácido 3-(4-{5-[4-ciclohexil-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico

5 Ácido 3-(4-{5-[4-[(1-metiletil)oxi]-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico

Ácido [4-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]acético

10 Ácido [4-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]acético

Ácido 3-(4-{5-[2'-fluoro-2-(trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico

15 Ácido 4-[4-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoico

Ácido 4-[4-(5-{3-cloro-4-[(trifluorometil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoico

20 Ácido 4-[4-(5-{5-cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoico

25 Ácido 4-(4-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)butanoico

Ácido 4-(4-{5-[2-(trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)butanoico

30 Ácido 3-(4-{5-[4-metiloxi-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico

Ácido 4-{4-[5-(3-ciano-4-[(1R)-1-metilpropil]oxi]fenil)-1,2,4-oxadiazol-3-il}-1H-indol-1-il}butanoico

35 Ácido 4-{4-[5-(3-ciano-4-[(1S)-1-metilpropil]oxi]fenil)-1,2,4-oxadiazol-3-il}-1H-indol-1-il}butanoico

- Ácido 3-(4-{5-[3-etil-4-(1-piperidinil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- 5 Ácido 3-{4-[5-(4-ciclohexil-3-etilfenil)-1,2,4-oxadiazol-3-il]-1H-indol-1-il}propanoico
- 10 Ácido 4-[4-(5-{3-bromo-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoico
- 15 Ácido 3-(4-{5-[4-(2-metilpropil)-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- 20 Ácido 4-(4-{5-[3-ciano-4-(2-metilpropil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)butanoico
- 25 Ácido 3-(3-cloro-4-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- 30 Ácido 3-(3-cloro-5-{5-[3-cloro-4-[(trifluorometil)oxi]fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- 35 Ácido 3-(3-cloro-5-{5-[3-cloro-4-(metiloxi)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico

- Ácido 3-(3-cloro-5-{5-[4-(metiloxi)-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- 5 Ácido 3-(3-cloro-5-{5-[3-cloro-4-(etiloxi)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- Ácido 3-[3-cloro-5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoico
- 10 Ácido 3-(3-cloro-5-{5-[4-nitro-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- Ácido 3-[3-cloro-5-(5-{4-cloro-3-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoico
- 15 Ácido 3-(3-cloro-5-{5-[6-(metiloxi)-3-bifenilil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- 3-(5-{5-[6-(trifluorometil)-3-bifenilil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- 20 Ácido 3-{5-[5-(4-fenil-2-tienil)-1,2,4-oxadiazol-3-il]-1H-indol-1-il}propanoico
- Ácido 3-{3-cloro-5-[5-(4-ciclohexilfenil)-1,2,4-oxadiazol-3-il]-1H-indol-1-il}propanoico
- 25 Ácido 3-(3-cloro-5-{5-[6-(4-fluorofenil)-3-piridinil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- Ácido 3-(3-cloro-5-{5-[6-(4-fluorofenil)-3-piridinil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- 30 o sus sales farmacéuticamente aceptables.

Los derivados farmacéuticamente aceptables de los compuestos de fórmula (I) incluyen cualquier sal farmacéuticamente aceptable, éster o sal de tal éster de un compuesto de fórmula (I) que, tras la administración al receptor, puede proporcionar

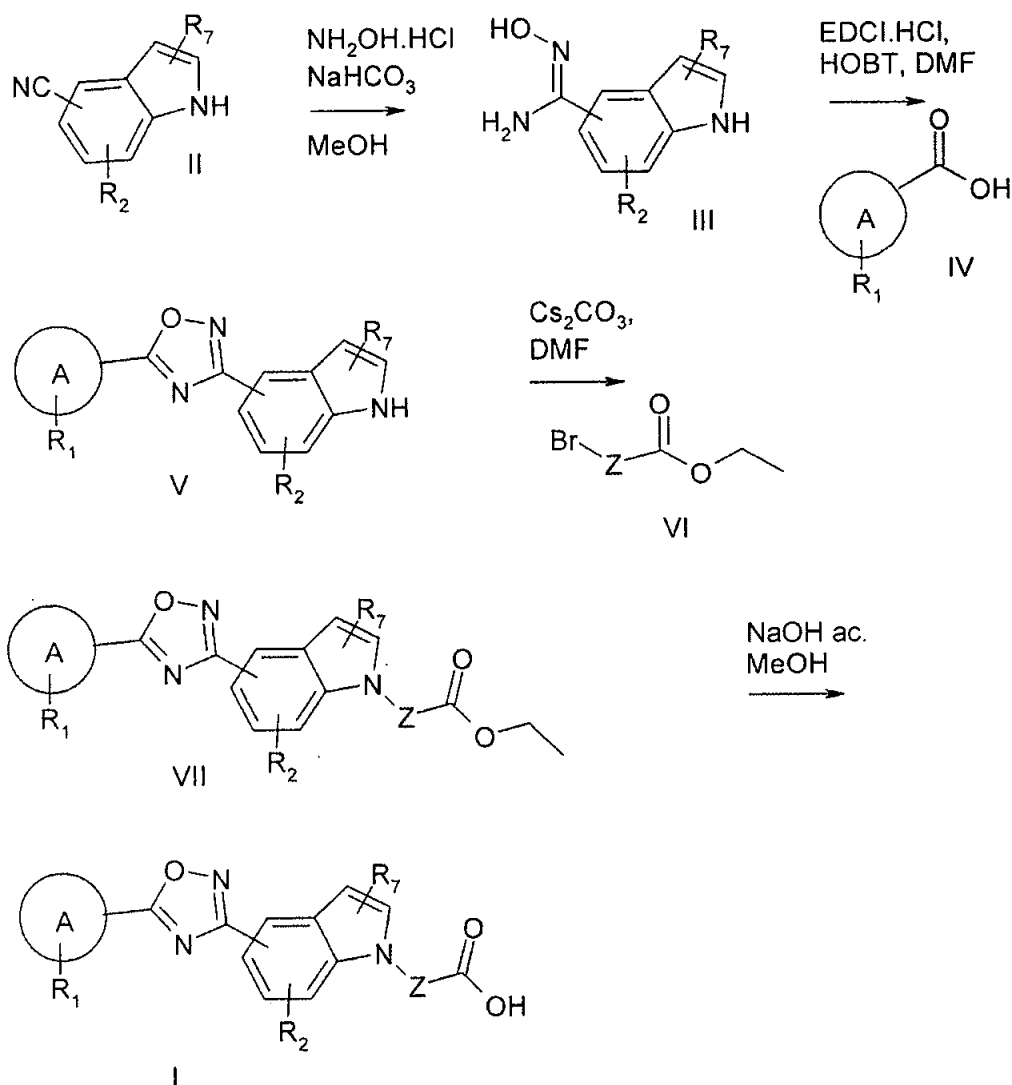
(directa o indirectamente) un compuesto de fórmula (I) o un metabolito activo o resto del mismo.

Los compuestos de fórmula (I) pueden formar sales. Será evidente que para su uso en medicina, las sales de los compuestos de fórmula (I) deberían ser farmacéuticamente aceptables. Las sales farmacéuticamente aceptables, adecuadas, serán evidentes para los expertos en la materia e incluyen las descritas en J. Pharm. Sci., 1977, 66, 1-19, tales como las sales de adición de ácido formadas con ácidos inorgánicos, por ejemplo, ácido clorhídrico, bromhídrico, sulfúrico, nítrico o fosfórico; y ácidos orgánicos, por ejemplo ácido succínico, maleico, acético, fumárico, cítrico, tartárico, benzoico, p-toluensulfónico, metansulfónico o naftalensulfónico. Ciertos compuestos de fórmula (I) pueden formar sales de adición de ácidos con uno o más equivalentes del ácido. La presente invención incluye dentro de su alcance todas las formas estequiométricas y no estequiométricas posibles. También se pueden preparar sales a partir de bases farmacéuticamente aceptables, incluidas bases orgánicas y bases inorgánicas. Las sales derivadas de bases inorgánicas incluyen sales de aluminio, amonio, calcio, cobre, férricas, ferrosas, de litio, de magnesio, sales mangánicas, manganosas, de potasio, de sodio, de cinc y similares. Las sales derivadas de bases orgánicas farmacéuticamente aceptables incluyen sales de aminas primarias, secundarias y terciarias; aminas sustituidas, incluidas las aminas sustituidas naturales; y las aminas cíclicas. Bases orgánicas farmacéuticamente aceptables convencionales incluyen arginina, betaína, cafeína, colina, N,N'-dibenciletilendiamina, dietilamina, 2-dietilaminoetanol, 2-dimetilaminoetanol, etanolamina, etilendiamina, N-etil-morfolina, N-etilpiperidina, glucamina, glucosamina, histidina, hidrabamina, isopropilamina, lisina, metilglucamina, morfolina, piperazina, piperidina, procaína, purinas, teobromina, trietilamina, trimetilamina, tripropilamina, tris(hidroximetil)aminometano (TRIS, trometamol) y similares. También se pueden formar sales a partir de resinas de intercambio iónico básicas, por ejemplo resinas de poliaminas. Cuando el compuesto de la presente invención es básico, pueden prepararse sales a partir de ácidos farmacéuticamente aceptables, incluyendo ácidos inorgánicos y orgánicos. Tales ácidos incluyen ácido acético, bencenosulfónico, benzoico, canforsulfónico, cítrico, etanosulfónico, etanodisulfónico, fumárico, glucónico, glutámico, bromhídrico, clorhídrico, isetiónico, láctico, maleico, málico, mandélico, metanosulfónico, mónico, pamoico, pantoténico, fosfórico, propiónico, succínico, sulfúrico, tartárico, p-toluenosulfónico y similares.

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

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

En un aspecto adicional, esta invención proporciona procedimientos para la preparación de un compuesto de Fórmula (I). En un aspecto, el compuesto de fórmula (I) se puede preparar por el procedimiento del Esquema I, donde A, Z, R₁, R₂, R₇ se definen igual que para la fórmula (I).



Esquema I

- La primera etapa del procedimiento (II a III) se lleva a cabo en un disolvente adecuado, tal como metanol o etanol y se calienta a una temperatura tal como 50-80°C. En la segunda etapa del procedimiento (III a V) los reactivos adecuados incluyen EDC.HCl y HOBT en un disolvente tal como DMF a una temperatura entre la temperatura ambiente y 90 °C o alternativamente PyBOP en DMF. Alternativamente (III) puede convertirse en (V) por tratamiento con el éster carboxílico de (IV) y etóxido de sodio en etanol en una reacción realizada bajo microondas a una temperatura tal como 120 °C. En la tercera etapa (V a VII) se usa una base tal como carbonato de cesio o alternativamente carbonato de potasio y la reacción se puede calentar ya sea de manera convencional o usando un reactor de microondas a una

temperatura tal como 140 °C. La cuarta etapa del proceso (VII a I) se lleva a cabo en un disolvente adecuado tal como metanol o alternativamente etanol y se puede llevar a cabo ya sea a temperatura ambiente o temperatura elevada tal como 40 o 50 °C.

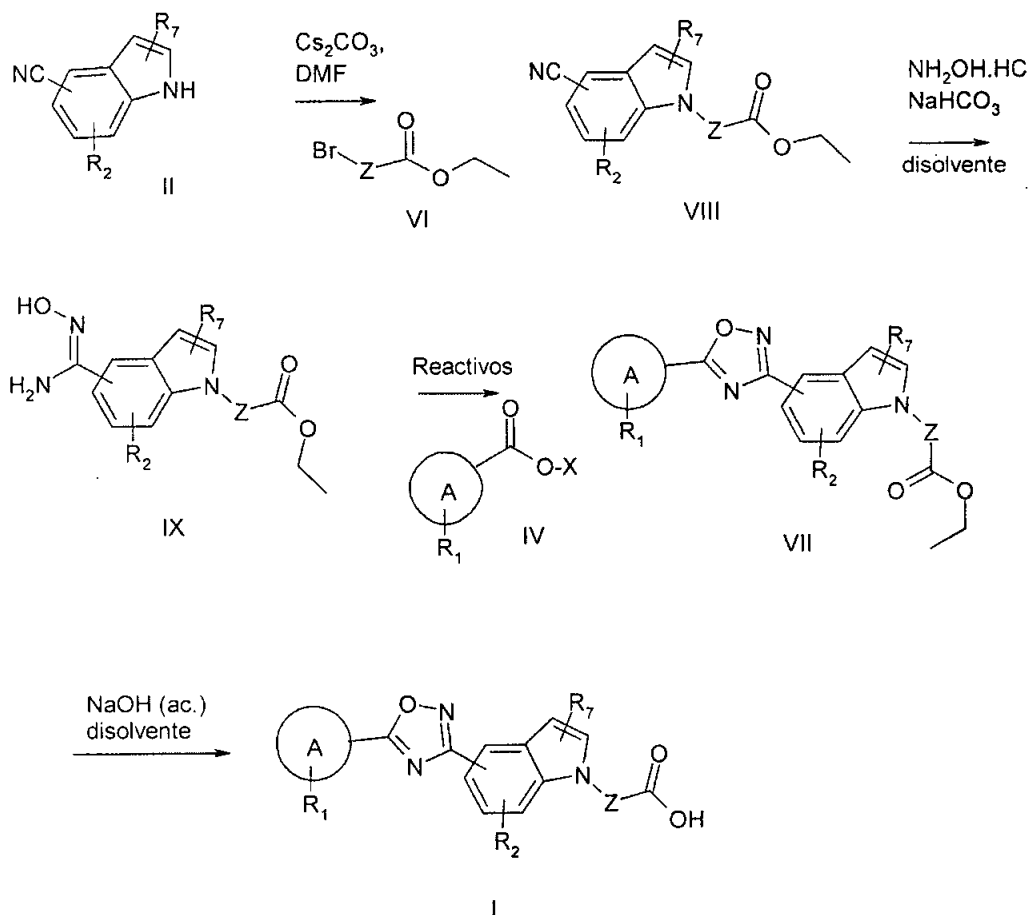
- 5 Los compuestos de fórmula (IV) o son disponibles comercialmente, o se pueden preparar usando métodos descritos en la bibliografía or se pueden preparar como se describe en la parte experimental de esta memoria. Los bromuros de fórmula (VI) están disponibles en el mercado o pueden prepararse usando métodos descritos en la bibliografía o usando los métodos descritos.

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En otro aspecto, el compuesto de fórmula (I) se puede preparar por el procedimiento del Esquema II, donde A, Z, R₁, R₂, R₇ se definen igual que para la fórmula (I). En la primera etapa, la reacción (II a VIII) se puede calentar a 80 °C. La segunda etapa del proceso (VIII a IX) se lleva a cabo en un disolvente adecuado tal como etanol o

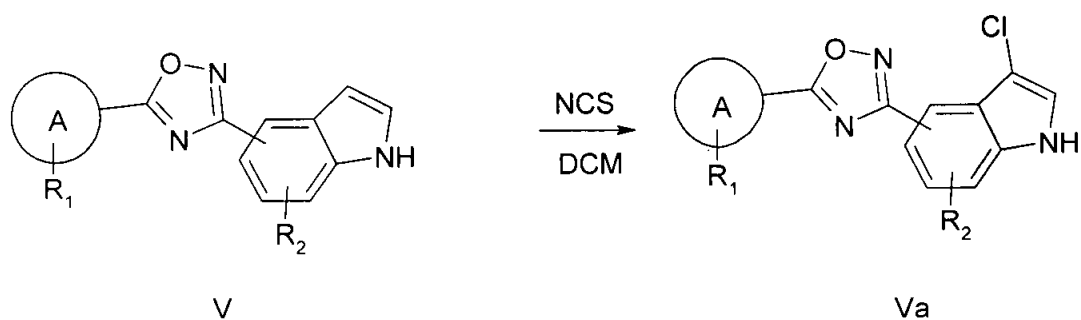
- 15 metanol. La tercera etapa de este proceso (IX a VII) requiere reactivos de acoplamiento amídico tales como EDC.HCl y HOBt en un disolvente tal como DMF a una temperatura entre la temperatura ambiente y 120 °C. La cuarta etapa del proceso se lleva a cabo en un disolvente adecuado tal como etanol o metanol. Los compuestos de fórmula (IV) o son disponibles comercialmente, o se pueden
- 20 preparar usando métodos descritos en la bibliografía or se pueden preparar como se describe en la parte experimental de esta memoria. Los bromuros de fórmula (VI) están disponibles en el mercado o pueden prepararse usando métodos descritos en la bibliografía o por los métodos descritos.

Esquema II



- 5 En los casos en que el sustituyente R_7 en la fórmula I es un átomo de cloro unido a C-3 del anillo de indol, este se puede introducir de diversas maneras. El intermedio (V) en el esquema I donde $R_7 = \text{H}$ y R_1 , R_2 y A se definen como en la fórmula (I) se pueden tratar con *N*-clorosuccinimida en diclorometano para generar el 3-cloro-compuesto (Va) que puede después convertirse en (I) como se describe en el
- 10 esquema I (Esquema III)

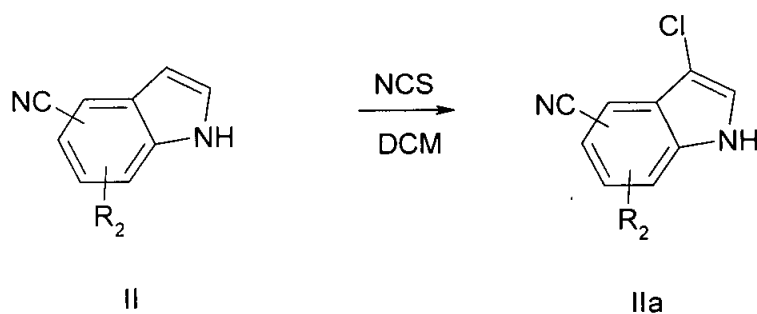
Esquema III



- 5 Alternativamente, el intermedio (II) donde R₇ = H se puede clorar por tratamiento con *N*-clorosuccinimida en DMF para generar un 3-cloro-indol (IIa) que puede convertirse en un compuesto de estructura (I) como se describe en el esquema II (Esquema IV).

Esquema IV

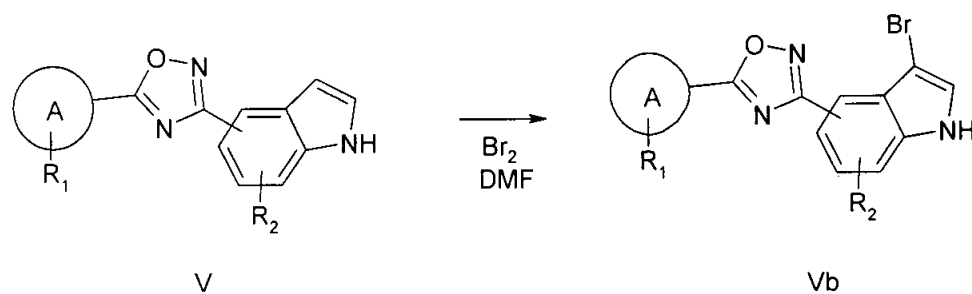
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Cuando R₇ = Br el Intermedio (V) donde R₇ = H y A, R₁ y R₂ son como se definen en la fórmula (I) se puede bromar por tratamiento con Br₂ en DMF para generar (Vb) donde R₇ = Br (Esquema V).

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Esquema V

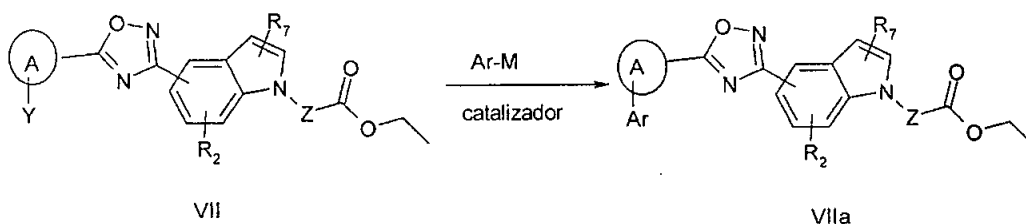


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- En los casos en que R_1 es un grupo fenilo es posible introducir este grupo por una reacción de trans-acoplamiento sobre un compuesto de estructura VII para generar VIIa (Esquema VI) donde A, Z, R_2 y R_7 son como se definen en la fórmula (I), y Ar es fenilo opcionalmente sustituido, seguida de hidrólisis para dar el compuesto I. En esta transformación, M es un grupo tal como $B(OH)_2$ que permite que ocurra la reacción de transacoplamiento, Y es un grupo tal como bromo, yodo o trifluorometanosulfonato y el catalizador es una especie de paladio tal como tetrakis(trifenilfosfina) paladio(0). Tales reacciones se llevan a cabo típicamente a temperatura elevada.

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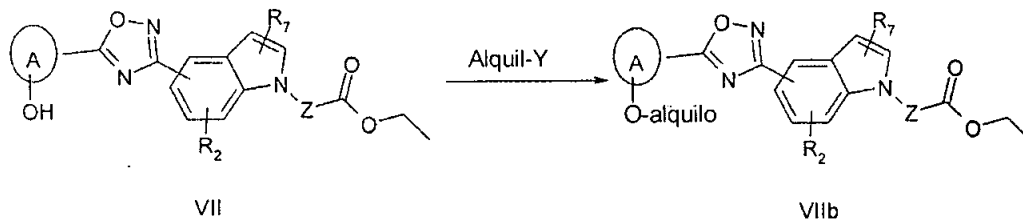
Esquema VI



- En los casos en que R_1 es un grupo alcoxi tal como O-etilo u O-isopropilo el sustituyente alquilo se puede introducir en un compuesto de fórmula VII donde $R_1 = OH$ y A, Z, R_7 y R_2 son como se definen en la fórmula (I) para generar un compuesto de fórmula VIIb donde $R_1 = O$ -alquilo (Esquema VII). En este caso Y es un halógeno tal como yodo. La reacción se puede realizar en un disolvente polar tal como DMF en presencia de una base tal como carbonato de potasio.

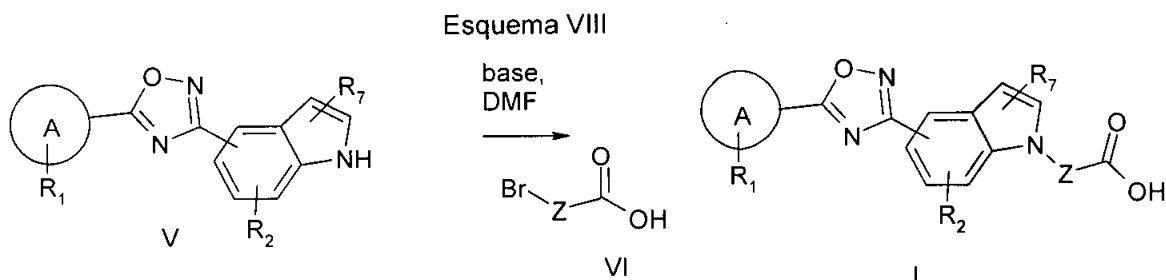
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Esquema VII



- En ciertos casos es posible alquilar el indol intermedio (V) donde R_1 , R_2 , R_7 y A son como se definen en la fórmula (I) directamente con el bromuro de alquilo sustituido con ácido carboxílico para generar el compuesto final (I) sin necesidad de una etapa

de hidrólisis (Esquema VIII). Una base adecuada para esta transformación es el carbonato de cesio.



Las sales farmacéuticamente aceptables se pueden preparar convencionalmente mediante reacción con el ácido o derivado de ácido apropiado.

- 10 Las potencias y eficacias de los compuestos de esta invención para el receptor S1P1 se pueden determinar por ensayo GTPγS realizado sobre el receptor humano clonado como se describe aquí o por el ensayo de unión a levadura, también descrito aquí. Los compuestos de fórmula (I) han demostrado actividad agonista en el receptor S1P1, usando los ensayos funcionales descritos aquí.

- 15 Los compuestos de fórmula (I) y sus sales farmacéuticamente aceptables son, por tanto, de utilidad en el tratamiento de afecciones o trastornos que están mediados por el receptor S1P1. En particular, los compuestos de fórmula (I) y sus sales farmacéuticamente aceptables son de utilidad en el tratamiento de esclerosis
- 20 múltiple, enfermedades autoinmunitarias, trastornos inflamatorios crónicos, asma, neuropatías inflamatorias, artritis, trasplantes, enfermedad de Crohn, colitis ulcerosa, lupus eritematoso, psoriasis, lesión por isquemia-reperfusión, tumores sólidos, y metástasis tumoral, enfermedades asociadas con angiogénesis, enfermedades
- 25 inflamatorias intestinales, diabetes insulín y no-insulín-dependientes (denominados aquí en lo sucesivo "Trastornos de la invención").

Debe entenderse que "tratamiento", como se usa en este documento, incluye tanto la profilaxis como el alivio de síntomas manifiestos.

30

De esta manera, la invención también proporciona un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, para uso como una sustancia

terapéutica, en particular, en el tratamiento de afecciones/trastornos que pueden mediarse por los receptores S1P1. En particular, la invención proporciona un compuesto de fórmula (I) o una de sus sales farmacéuticamente aceptables para uso como sustancia terapéutica en el tratamiento de esclerosis múltiple, enfermedades autoinmunitarias, trastornos inflamatorios crónicos, asma, neuropatías inflamatorias, artritis, trasplantes, enfermedad de Crohn, colitis ulcerosa, lupus eritematoso, psoriasis, lesión por isquemia-reperfusión, tumores sólidos, y metástasis tumoral, enfermedades asociadas con angiogénesis, enfermedades vasculares, afecciones dolorosas, enfermedades víricas agudas, afecciones inflamatorias intestinales, diabetes insulín y no-insulín-dependientes. La invención además proporciona un método de tratamiento de afecciones o trastornos en mamíferos, incluyendo seres humanos, que pueden estar mediados por el receptor S1P1, que comprende administrar al individuo que padece la afección o el trastorno una cantidad terapéuticamente segura y eficaz de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo.

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

Para usar los compuestos de Fórmula (I) y sus sales farmacéuticamente aceptables en terapia, normalmente se formularán en una composición farmacéutica de acuerdo con la práctica farmacéutica convencional. La presente invención proporciona también una composición farmacéutica, que comprende un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, y un portador o excipiente farmacéuticamente aceptable.

En un aspecto adicional, la presente invención proporciona un procedimiento para preparar una composición farmacéutica, procedimiento que comprende mezclar un compuesto de fórmula (I) o una de sus sales farmacéuticamente aceptables y un vehículo o excipiente farmacéuticamente aceptable.

Una composición farmacéutica de la invención, que puede prepararse por mezcla, adecuadamente a temperatura ambiente y a presión atmosférica, se adapta normalmente para administración oral, parenteral o rectal y, como tal, puede estar

en forma de comprimidos, cápsulas, preparaciones líquidas orales, polvos, gránulos, pastillas, polvos reconstituibles, disoluciones o suspensiones inyectables o infundibles o supositorios. Se prefieren generalmente las composiciones administrables oralmente.

5

Los comprimidos y cápsulas para administración oral pueden estar en forma de unidades de dosificación y pueden contener excipientes convencionales, tales como agentes aglutinantes (por ejemplo, almidón de maíz pregelatinizado, polivinilpirrolidona o hidroxipropilmetilcelulosa); cargas (por ejemplo, lactosa, 10 celulosa microcristalina o hidrógeno-fosfato cálcico); lubricantes para fabricar comprimidos (por ejemplo, estearato de magnesio, talco o sílice); disgregantes (por ejemplo, almidón de patata o glicolato sódico de almidón); y agentes humectantes aceptables (p. ej., laurilsulfato sódico). Los comprimidos se pueden recubrir de acuerdo con métodos bien conocidos en la práctica farmacéutica clásica.

15

Las preparaciones líquidas orales pueden estar, por ejemplo, en forma de suspensiones, disoluciones, emulsiones, jarabes o elixires acuosos u oleosos, o pueden estar en forma de un producto seco para reconstituirlo con agua u otro vehículo adecuado antes de su uso. Tales preparaciones líquidas pueden contener 20 aditivos convencionales tales como agentes de suspensión (p. ej., jarabe de sorbitol, derivados de celulosa o grasas comestibles hidrogenadas), agentes emulsionantes (p. ej., lecitina o goma arábica), vehículos no acuosos (que pueden incluir aceites comestibles, p. ej., aceite de almendras, ésteres oleosos, alcohol etílico o aceites vegetales fraccionados), conservantes (p. ej., p-hidroxibenzoatos de metilo o propilo 25 o ácido sórbico) y, si se desea, agentes saporíferos o colorantes convencionales, sales tamponantes y agentes edulcorantes en la medida apropiada. Las preparaciones para administración oral pueden formularse adecuadamente para dar una liberación controlada del compuesto activo.

30 Para administración parenteral, se preparan formas farmacéuticas unitarias fluidas utilizando un compuesto de la invención o sales farmacéuticamente aceptable del mismo y un vehículo estéril. Las formulaciones para inyección pueden presentarse en una forma de dosificación unitaria, por ejemplo, en ampollas o en multi-dosis, que utilizan un compuesto de la invención o derivados farmacéuticamente aceptables del mismo y un vehículo estéril, opcionalmente con un conservante añadido. Las 35 composiciones pueden tomar formas tales como suspensiones, disoluciones o

emulsiones en vehículos oleosos o acuosos, y pueden contener agentes de formulación tales como agentes de suspensión, estabilizantes y/o dispersantes. Como alternativa, el ingrediente activo puede estar en forma de polvo para reconstituirse con un vehículo adecuado, p. ej. agua estéril apirogénica, antes de su uso. El compuesto, dependiendo del vehículo y la concentración usados, puede estar suspendido o disuelto en el vehículo. En la preparación de disoluciones, el compuesto se puede disolver para inyección y esterilizar por filtración antes de cargarlo en un vial o ampolla adecuado y sellarlo. De manera ventajosa, se disuelven en el vehículo coadyuvantes tales como anestésicos locales, conservantes o agentes de tamponamiento. Para mejorar la estabilidad, la composición puede congelarse después de cargarse en el vial y el agua puede retirarse al vacío. Las suspensiones parenterales se preparan esencialmente de la misma manera, con la excepción de que el compuesto se suspende en el vehículo en lugar de disolverse, y la esterilización no puede efectuarse por filtración. El compuesto se puede esterilizar por exposición a óxido de etileno antes de ser suspendido en un vehículo estéril. Ventajosamente, se incluye un tensioactivo o agente humectante en la composición para facilitar la distribución uniforme del compuesto.

Pueden formularse lociones con una base acuosa u oleosa y, en general, contendrán también uno o más agentes emulsionantes, agentes estabilizantes, agentes dispersantes, agentes de suspensión, agentes espesantes o agentes colorantes. Pueden formularse gotas con una base acuosa o no acuosa que también comprenden uno o más agentes dispersantes, agentes estabilizantes, agentes solubilizantes o agentes de suspensión. Pueden contener también un conservante.

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

Los compuestos de fórmula (I) o sus sales farmacéuticamente aceptables también se pueden formular como preparaciones de actividad prolongada. Estas formulaciones de actuación prolongada pueden administrarse por implantación (por ejemplo, por vía subcutánea o por vía intramuscular) o por inyección intramuscular. De esta manera, por ejemplo, los compuestos de la invención pueden formularse con materiales poliméricos o hidrófobos adecuados (por ejemplo, como una

emulsión en un aceite aceptable) o resinas de intercambio iónico o como derivados poco solubles, por ejemplo, como una sal poco soluble.

Para la administración intranasal, los compuestos de fórmula (I) o sus sales farmacéuticamente aceptables pueden formularse como disoluciones para administración por medio de un dispositivo de dosis medidas o de dosis unitarias o, como alternativa, como una mezcla en polvo con un vehículo adecuado para administración usando un dispositivo de liberación adecuado. De esta manera, los compuestos de fórmula (I) o sus sales farmacéuticamente aceptables pueden formularse para administración oral, bucal, parenteral, tópica (incluyendo oftálmica y nasal), de liberación retardada o rectal o en una forma adecuada para administración por inhalación o aspiración (a través de la boca o de la nariz).

Los compuestos de fórmula (I) o sus sales farmacéuticamente aceptables pueden formularse para administración tópica en forma de pomadas, cremas, geles, lociones, supositorios vaginales, aerosoles o gotas (por ejemplo, gotas oculares, para los oídos o nasales). Los ungüentos y cremas se pueden formular, por ejemplo, con una base acuosa u oleosa con la adición de agentes espesantes y/o gelificantes adecuados. Las pomadas para administración oftálmica se pueden fabricar de 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 usada en el tratamiento de los trastornos mencionados anteriormente variará de manera usual con la gravedad de los trastornos, el peso del que los sufre, y otros factores similares. Sin embargo, como norma 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 fórmula (I) o sus sales farmacéuticamente aceptables se pueden usar en preparaciones de combinación. Por ejemplo, los compuestos de la invención se pueden usar en combinación con ciclosporina A, metotrexato, esteroides, rapamicina, inhibidores de las citocinas proinflamatorias, inmunomoduladores, incluyendo materiales biológicos u otros compuestos terapéuticamente activos.

177

La presente invención también incluye compuestos marcados con isótopos, que son idénticos a los citados en las fórmulas I y siguientes salvo en que uno o más átomos se han reemplazado por un átomo que tiene una masa atómica o número másico diferente de la masa atómica o número másico encontrado habitualmente en la naturaleza. Los ejemplos de isótopos que pueden incorporarse en compuestos de la invención incluyen isótopos de hidrógeno, carbono, nitrógeno, oxígeno, fósforo, flúor, yodo y cloro, tales como ^3H , ^{11}C , ^{14}C , ^{18}F , ^{123}I y ^{125}I .

Dentro del alcance de la presente invención se encuentran compuestos de la presente invención y sales farmacéuticamente aceptables de dichos compuestos que contienen los isótopos mencionados anteriormente y/u otros isótopos de otros átomos. Los compuestos marcados con isótopos de la presente invención, por ejemplo aquellos en los que se incorporan isótopos radioactivos tales como ^3H o ^{14}C son útiles en ensayos de distribución de fármacos y/o sustratos en tejidos. Se prefieren particularmente los isótopos tritio, es decir ^3H , y carbono-14, es decir, ^{14}C , por su facilidad de preparación y detectabilidad. Los isótopos ^{11}C y ^8F son particularmente útiles en PET (tomografía de emisión de positrones), y los isótopos ^{125}I son particularmente útiles en SPECT (tomografía computerizada de emisión de un solo fotón), todos útiles en la formación de imágenes del cerebro. Además, la sustitución con isótopos más pesados, tales como deuterio, es decir ^2H , puede producir ciertas ventajas terapéuticas debidas a una mayor estabilidad metabólica, por ejemplo una mayor semivida *in vivo* o menores requisitos de dosificación y, por lo tanto, pueden preferirse en algunas circunstancias. Los compuestos marcados con isótopos de fórmula (I) y siguientes de esta invención pueden prepararse, en general, realizando los procedimientos descritos en los esquemas y/o en los ejemplos que se muestran a continuación, sustituyendo un reactivo no marcado con isótopos por un reactivo marcado con isótopos fácilmente adquirible.

Todas las publicaciones, incluyendo, aunque sin limitarse a ello, las patentes y solicitudes de patentes mencionadas en esta memoria, se incorporan a la presente como referencia como si se indicara específica e individualmente que cada publicación individual se incorpora a la presente como referencia como si estuviera expuesta en su totalidad.

Las siguientes Descripciones y Ejemplos ilustran la preparación de compuestos farmacológicamente activos de la invención.

Condiciones, hardware y software para Sistemas de LCMS Analíticos**Hardware**

- Bomba de gradiente Agilent 1100
- 5 Autoinyector Agilent 1100
- Detector Agilent 1100 DAD
- Desgasificador Agilent 1100
- Estufa Agilent 1100
- Controlador Agilent 1100
- 10 Gestor de disolvente binario Waters Acquity
- Gestor de muestras Waters Acquity
- PDA Waters Acquity
- Espectrómetro de Masas Waters ZQ
- Sedere Sedex 55, Sedere Sedex 85, Sedere Sedex 75 o Polymer Labs PL-ELS-
- 15 2100

Software

Waters MassLynx versión 4.0 SP2 o versión 4.1

Para el método de 5 minutos**20 Columna:**

La columna usada es una Waters Atlantis, cuyas dimensiones son 4,6 mm x 50 mm.

El tamaño de partículas de la fase estacionaria es de 3 µm.

Disolventes

A: Disolvente acuoso = agua + ácido fórmico al 0,05%

- 25 B: Disolvente orgánico = Acetonitrilo + ácido fórmico al 0,05%

Método

El método genérico usado tiene un tiempo de ejecución de 5 minutos.

	Tiempo/min	%B
	0	3
30	0,1	3
	4	97
	4,8	97
	4,9	3
	5,0	3

35 Caudal

El método anterior tiene un caudal de 3 ml/min

Para el método de 2 minutos**Software**

40

Waters Masslynx versión 4.1

Columna:

La columna usada es una Waters Acquity BEH UPLC C18, cuyas dimensiones son 2,1 mm x 50 mm. El tamaño de partículas de la fase estacionaria es de 1.7 μm .

5 Disolventes

A: Disolvente acuoso = agua + ácido fórmico al 0,05%

B: Disolvente orgánico = Acetonitrilo + ácido fórmico al 0,05%

Lavado débil = 1:1 Metanol : Agua

10 Lavado fuerte = Agua

Método

El método genérico usado tiene un tiempo de ejecución de 2 minutos.

15

Tiempo / min	%B
0	3
0,1	3
1,5	97
1,9	97
2,0	3

El método anterior tiene un caudal de 1 ml/min.

El volumen de inyección para el método genérico es 0,5 μl .

La temperatura de la columna es de 40 grados.

20 El intervalo de detección UV es de 220 a 330 nm

Sistema Auto Prep dirigido por masas de acceso abierto (MDAP)

25 **Hardware**

Los instrumentos Prep dirigidos por masas de acceso abierto consisten en los siguiente:

1 bomba de gradiente Waters 600

1 inyector / colector Waters 2767

30 1 gestor de reactivos Waters

1 Espectrómetro de masas Micromass ZQ

1 Colector de residuos Gilson Aspec

1 Detector de UV post-fracción Gilson 115

1 sistema Computer.

35 **Software**

Waters MassLynx v4,0

Columna:

La columna usada típicamente es una columna Supelco LCABZ+ cuyas dimensiones son 20 mm de diámetro interno por 100 mm de longitud. El tamaño de partículas de la fase estacionaria es 5 µm.

Disolventes

- 5 A: Disolvente acuoso = agua + ácido fórmico al 0,1%
B: Disolvente orgánico = MeCN: agua 95:5 + ácido fórmico al 0,05%
Disolvente de constitución = MeOH: agua 80:20 + acetato amónico 50 mM
Disolvente de aclarado de la aguja = MeOH: Agua: DMSO 80:10:10

Métodos

- 10 Se puede usar uno de cinco métodos dependiendo del tiempo de retención analítico del compuesto de interés.
Todos tienen un tiempo de ejecución de 15 minutos, que comprende un gradiente de 10 minutos seguido de un lavado abundante de la columna de 5 minutos y una etapa de re-equilibrado.
- 15 MDP 1,5-2,2 = 0-30% de B
MDP 2,0-2,8 = 5-30% de B
MDP 2,5-3,0 = 15-55% de B
MDP 2,8-4,0 = 30-80% de B
MDP 3,8-5,5 = 50-90% de B

20 Caudal

Todos los métodos anteriores tienen un caudal de 20ml/min.

Sistema alternativo:

- 25 Hardware
- Módulo de Gradiente Binario Waters 2525
 - Bomba de Preparación Waters 515
 - Módulo de Control de Bomba Waters
- 30
- Colector de Inyección Waters 2767
 - Conductor de Fluidos de la Columna Waters
 - Detector de Serie de Fotodiodos Waters 2996
 - Espectrómetro de Masas Waters ZQ
 - Colector de fracciones Gilson 202
- 35
- Colector de residuos Gilson Aspec

Software

Waters Masslynx versión 4 SP2

40

Columna:

Las columnas usadas son Waters Atlantis, cuyas dimensiones son 19 mm x 100 mm (escala pequeña) y 30 mm x 100 mm (escala grande). El tamaño de partículas de la fase estacionaria es de 5m m.

5 Disolventes

A: Disolvente acuoso = agua + ácido fórmico al 0,1%

B: Disolvente orgánico = Acetonitrilo + ácido fórmico al 0,1%

Disolvente de preparación = Metanol : agua

10 Disolvente de aclarado de agujas = Metanol

Métodos

15 Se usan cinco métodos dependiendo del tiempo de retención analítico del compuesto de interés. Todos tienen un tiempo de ejecución de 13,5 minutos, que comprende un gradiente de 10 minutos seguido de un lavado abundante de la columna de 3,5 minutos y una etapa de re-equilibrado.

20 Escala Grande/Pequeña 1,0-1,5 = 5-30% de B

Escala Grande/Pequeña 1,5-2,2 = 15-55% de B

Escala Grande/Pequeña 2,2-2,9 = 30-85% de B

25 Escala Grande/Pequeña 2,9-3,6 = 50-99% de B

Escala Grande/Pequeña 3,6-5,0 = 80-99% de B (en 6 minutos seguida de lavado abundante de 7,5 minutos y re-equilibrado)

30

Caudal

Todos los métodos anteriores tienen un caudal de 20 ml/min (Small Scale) o 40 ml/min (Large Scale)

35

Gradientes poco escalonados

Amplitud 1,5 a 2,3 min = 13-29% B

Amplitud 1,9 a 2,3 min = 25-41% B

40

Amplitud 2,3 a 2,6 min = 37-53% B

Amplitud 2,6 a 3,1 min = 49-65% B

Amplitud 3,1 a 3,6 min = 61-77% B

Condiciones usadas para la RMN

5 **Hardware**

Bruker 400 MHz Ultrashield
Automuestreador Bruker B-ACS60
Consola Bruker Advance 400
Bruker DPX250

10 Bruker AVANCE 500

Bruker DRX600

Software

Interfase del usuario - RMN Kiosk
Software de control - XWin RMN versión 3.0

15

Cromatografía

Salvo indicación en contrario, toda la cromatografía se llevó a cabo usando columnas de sílice

20

Abreviaturas:

g – gramos

mg - miligramos

ml – mililitros

25 ul – microlitros

MeCN - acetonitrilo

MeOH - metanol

EtOH - etanol

Et₂O - éter dietílico

30 EtOAc - acetato de etilo

DCM - diclorometano

DIAD – azodicarboxilato de diisopropilo

DME – 1,2-bis(metiloxi)etano

DMF – N,N-dimetilformamida

35 DMSO - dimetilsulfóxido

EDAC - hidrocloreuro de N-(3-dimetilaminopropil)-N'-etilcarbodiimida

EDC - hidrocloreuro de N-(3-dimetilaminopropil)-N'-etilcarbodiimida

EDCI - hidrocloreuro de N-(3-dimetilaminopropil)-N'-etilcarbodiimida

HOBT/HOBt – Hidroxibenzotriazol

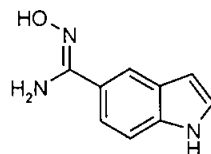
	IPA –	alcohol isopropílico
	NCS –	N-clorosuccinimida
	PyBOP –	Hexafluorofosfato de benzotriazol-1-il-oxitripirrolidinofosfonio
	THF –	tetrahidrofurano
5	dba –	dibenciliden acetona
	ta –	temperatura ambiente
	°C –	grados Celsius
	M –	Molar
	H –	protón
10	s –	singlete
	d –	doblete
	t –	triplete
	q –	cuartete
	MHz –	megahertzios
15	MeOD –	metanol deuterado
	LCMS –	Cromatografía líquida / Espectrometría de masas
	LC/MS –	cromatografía líquida/espectrometría de masas
	MS –	Espectrometría de masas
	ES –	Electropulverización
20	MH ⁺ –	ion de masas + H ⁺
	MDAP –	cromatografía líquida preparativa automatizada dirigida por masas.
	sat. –	saturado

25 Sección de química general

Cabe la posibilidad de que los intermedios para la preparación de los ejemplos no se hayan preparado necesariamente a partir del lote específico descrito.

Descripción para D1

30 ***N*-Hidroxi-1*H*-indol-5-carboximidamida (D1)**

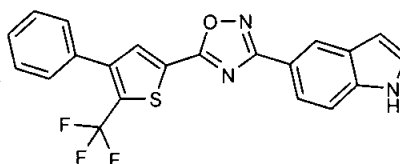


5-Cianoindol (1,00 g), hidroxilamina.HCl (978 mg) y NaHCO₃ (2,95 g) se disolvieron/suspendieron en MeOH (14 ml), se calentaron a 50 °C y se agitaron

durante una noche. El análisis LCMS indicó que la reacción era incompleta después de este tiempo, así que se añadió otra porción de hidroxilamina.HCl (978 mg) y la temperatura de la reacción se elevó a 80 °C. Después de 4 horas, la reacción se completó. La mezcla de reacción se enfrió a temperatura ambiente y se evaporó hasta sequedad a presión reducida. El residuo se trató con HCl acuoso 1 M (50 ml) y se extrajo con EtOAc (2 x 50 ml). Esto no logró extraer el producto de la solución acuosa así que se trató con NaOH acuoso 2M para ajustar el pH aproximadamente a 7 y después se extrajo de nuevo con EtOAc (3 x 50 ml). Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre MgSO₄, se filtraron y se evaporaron hasta sequedad para producir el compuesto del título en forma de un aceite pardo (1,36 g). δ H (MeOD, 400MHz) 6,50 (1H, s), 7,27 (1H, s), 7,36-7,45 (2H, m), 7,88 (1H, s). MS (ES): C₉H₈N₃O requiere 175; encontrado 176 (MH⁺).

15 **Descripción para D2**

5-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol (D2)

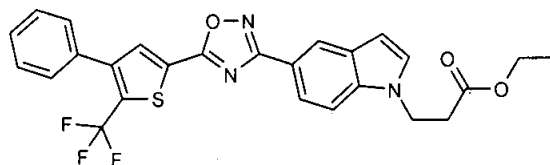


D1 (174 mg) y 4-fenil-5-(trifluorometil)-2-tiofenocarboxilato (286 mg) se combinaron, trataron con etóxido de sodio (21 % peso en EtOH, 411 ul) y calentaron a 120 °C en un reactor de microondas durante 30 minutos. El análisis LCMS indicó que la reacción era incompleta, así que se continuó calentando con microondas durante dos periodos adicionales de 30 minutos. Después, la mezcla de reacción se enfrió a RT, se inactivó con H₂O (2 ml) y se evaporó hasta sequedad a presión reducida para dar el producto bruto (411 mg) en forma de un sólido pardo. El residuo bruto se purificó en un cartucho 40+S Biotage, eluyendo con una mezcla del 0 al 50 % de Et₂O en éter de petróleo. Esto dio el compuesto del título (122 mg) en forma de un sólido blanquecino. δ H (CDCl₃, 400MHz): 6,68 (1H, s), 7,30 (1H, t), 7,41-7,55 (6H, m), 7,92 (1H, s), 7,99 (1H, d), 8,36 (1H, s ancho), 8,50 (1H, s). MS (ES): C₂₁H₁₂F₃N₃OS requiere 411; encontrado 410 (M-H⁺).

30

Descripción para D3

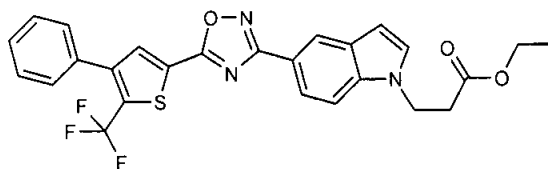
3-(5-{5-[4-Fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de etilo (D3)



D2 (100 mg) se disolvió en DMF (1,2 ml), se trató con K_2CO_3 (50 mg) después con 3-bromopropionato de etilo (90 mg) y se calentó a 130 °C durante una noche. Al cabo de este tiempo la LCMS indicó que la reacción era incompleta, así que se
5 añadió más 3-bromopropionato de etilo (45 mg) y se continuó agitando a 130 °C durante 2 horas. La LCMS no indicó ningún cambio, así que la mezcla de reacción se evaporó y después se repartió entre DCM y H_2O . La capa orgánica se separó y la fase acuosa se extrajo con DCM. Los extractos orgánicos combinados se secaron sobre $MgSO_4$, y se evaporaron para dar el producto deseado (148 mg). Este se
10 purificó sobre un cartucho de sílice (25+S), eluyendo con una mezcla del 0 al 25% de EtOAc en éter de petróleo y después nuevamente sobre un cartucho 25+M con una mezcla del 0 al 30% de EtOAc en éter de petróleo para dar el compuesto del título MF105672-144A3 (38 mg) en forma de un sólido blanco. δH ($CDCl_3$, 400MHz): 1,21 (3H, t), 2,85 (2H, t), 4,12 (2H, q), 4,50 (2H, t), 6,60 (1H, d), 7,21 (1H, d), 7,42-
15 7,52 (6H, m), 7,91 (1H, s), 8,00 (1H, d), 8,46 (1H, s). EM (ES+): $C_{26}H_{20}F_3N_3O_3S$ requiere 511; encontrado 512 (MH^+).

Descripción para D3 (Procedimiento alternativo)

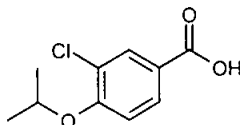
3-(5-{5-[4-Fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de etilo (D3)
20



5-{5-[4-Fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol (D2) (600 mg), 3-bromopropanoato de etilo (374 μl), carbonato de cesio (950 mg) y DMF se calentaron a 140 °C durante 1 hora en un reactor de microondas. Se añadió 1 eq.
25 adicional de 3-bromopropanoato de etilo (187 μl) y la mezcla se calentó durante 30 minutos. Después, la mezcla de reacción se evaporó, disolvió en DCM y filtró para dar el compuesto del título (650 mg) en forma de un sólido pardo. δH ($CDCl_3$, 400MHz): 1,21 (3H, t), 2,85 (2H, t), 4,13 (2H, q), 4,50 (2H, t), 6,61 (1H, d), 7,22 (1H,

d), 7,44-7,52 (6H, m), 7,89-7,92 (1H, m), 7,98-8,02 (1H, m), 8,45-8,46 (1H, m). MS (ES): $C_{26}H_{20}F_3N_3O_3S$ requiere 511; encontrado 512 (MH^+).

Descripción para D4 Ácido 3-cloro-4-[(1-metiletil)oxi]benzoico (D4)

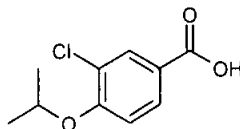


5

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 de la adición gota a gota de DIAD (9,44 ml) y se agitó a TA durante una noche. Después, la mezcla de reacción se evaporó y purificó sobre cartuchos de sílice (4 x 100 g), eluyendo con una mezcla del 0 al 40% de EtOAc en pentano para dar el producto bruto (7,00 g) en forma de un aceite incoloro. Este se disolvió en MeOH (30 ml) y NaOH acuoso 2 M (30 ml) y se agitó a TA durante un fin de semana. Después, la mezcla de reacción se evaporó y re-disolvió en H_2O . Esta solución se lavó con Et_2O , se aciduló hasta pH = 1 y se extrajo con Et_2O . Estos últimos extractos se secaron sobre $MgSO_4$, se filtraron y se evaporaron para dar el compuesto del título (4,16 g) en forma de un sólido blanco; δH (MeOD, 400MHz): 1,37 (6H, d), 4,77 (1H, septete), 7,12 (1H, d), 7,90 (1H, d), 7,98 (1H, s). MS (ES): $C_{10}H_{11}ClO_3$ requiere 214; encontrado 215 (MH^+).

20 Síntesis alternativa:

Ácido 3-cloro-4-[(1-metiletil)oxi]benzoico (D4)



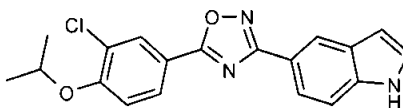
Metil-4-hidroxi-3-cloro benzoato de metilo (13,4 g) se disolvió en DMF (150 ml), se trató con K_2CO_3 (19,9 g) seguido de bromuro de isopropilo (13,5 ml) y la mezcla resultante se calentó a 70 °C y se agitó durante una noche. Después, la mezcla de reacción se enfrió a RT, se evaporó hasta sequedad, re-disolvió en EtOH, filtró y evaporó una vez más para dar el éster intermedio (22,2 g) en forma de un sólido blanco. Este compuesto era una mezcla de los ésteres metílico y etílico y se usó en bruto en la siguiente reacción.

30 El producto intermedio bruto (22,2 g) se disolvió en MeOH (75 ml), se trató con NaOH acuoso 2M (75 ml), se calentó a 60 °C y se agitó durante 2 horas. Después,

la mezcla de reacción se enfrió a RT, el MeOH se evaporó y la solución acuosa residual se aciduló con HCl acuoso 5M (30 ml). El precipitado se separó por filtración y se secó para dar el compuesto del título (15,1 g) en forma de un sólido blanco. δ H (CDCl₃, 400MHz): 1,42 (6H, d), 4,70 (1H, septet), 6,97 (1H, d), 7,97 (1H, d), 8,12 (1H, s). MS (ES): C₁₀H₁₁ClO₃ requiere 214; encontrado 213 (M-H⁺).

Descripción para D5 MF105672-175A2

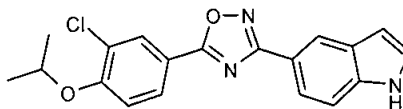
5-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol (D5)



D1 (500 mg), D4 (611 mg) y PyBOP (1,66 g) se disolvieron en DMF y se agitó durante una noche. Después, la mezcla de reacción se evaporó y se repartió entre EtOAc y H₂O. La capa orgánica se lavó con H₂O (x 2) y después con salmuera, se secó sobre MgSO₄, se filtró y se evaporó para dar el producto bruto. Este se purificó sobre un cartucho de sílice, eluyendo con una mezcla del 0 al 50% de Et₂O en hexano para dar el compuesto del título (120 mg) en forma de un sólido blanco. δ H (CDCl₃, 400MHz): 1,43 (6H, d), 4,69 (1H, septet), 6,92 (1H, s), 7,04 (1H, d), 7,25 (1H, s), 7,48 (1H, d), 8,00 (1H, d), 8,07 (1H, d), 8,25 (1H, s), 8,39 (1H, s ancho), 8,50 (1H, s). MS (ES): C₁₉H₁₆ClN₃O₂ requiere 353; encontrado 354 (MH⁺).

Descripción para D5 (Procedimiento alternativo)

5-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol (D5)



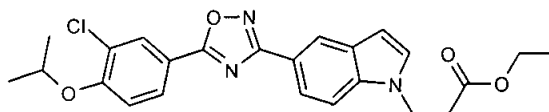
Una mezcla de 5-cianoindol (5,00 g), NH₂OH.HCl (6,11 g) y NaHCO₃ (14,77 g) en EtOH (176 ml) se calentó a 70 °C en atmósfera de Ar durante una noche y después a 80 °C durante 2,5 horas. Después, la mezcla de reacción se filtró y evaporó para dar un sólido amarillo anaranjado (material bruto D1).

D4 (7,55 g), HOBT (5,23 g) y EDCI (7,42 g) se disolvieron en DMF (88 ml). Esta mezcla se agitó durante 10 minutos y después se añadió el sólido amarillo anaranjado de antes (6,16 g) disuelto en DMF (88 ml). La mezcla de reacción se calentó a 80 °C durante una noche, después se evaporó y se repartió entre EtOAc y

H₂O. Las fases se separaron y la solución acuosa se extrajo con dos porciones adicionales de EtOAc. Las soluciones orgánicas combinadas se secaron y se evaporaron. Parte del residuo bruto se purificó en un cartucho 40+M Biotage, eluyendo con una mezcla del 5 al -30 % de EtOAc en hexano. Esto dio el compuesto del título(1,45 g) en forma de un sólido blanquecino. δ H (CDCl₃, 400MHz): 1,45 (6H, d), 4,72 (1H, septete), 6,66-6,69 (1H, m), 7,06 (1H, d), 7,29 (1H, triplete o dd aparente), 7,50 (1H, d), 8,01 (1H, dd), 8,08 (1H, dd), 8,27 (1H, d), 8,49-8,52 (1H, m). MS (ES): C₁₉H₁₆ClN₃O₂ requiere 353; encontrado 354 (MH⁺). El residuo bruto remanente se trituró con MeOH frío para dar el compuesto del título (3,54 g) en forma de un sólido blanquecino. Datos MS como los de antes.

Descripción para D6

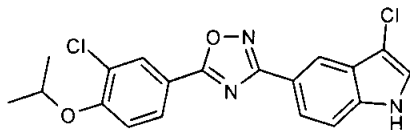
3-[5-(5-{3-Cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoato de etilo (D6)



D5 (100 mg) se disolvió en DMF (1,5 ml). A esta solución, se añadió K₂CO₃ (58 mg) seguido de 3-bromopropionato de etilo (72 ul) y la mezcla se agitó y se calentó a 100 °C. Después de 1 hora sólo se observó 5% de conversión por LCMS, así que se añadieron porciones adicionales de K₂CO₃ (97 mg) y 3-bromopropionato de etilo (72 ul). Después de 3 horas la mezcla de reacción se evaporó y después se repartió entre DCM y H₂O. La capa acuosa se extrajo con DCM después las soluciones en DCM combinadas se lavaron con salmuera, se secaron sobre MgSO₄, filtraron y evaporaron para dar el producto bruto. Este se purificó sobre un cartucho de sílice, eluyendo con una mezcla del 0 al 50% de Et₂O en éter de petróleo. Esto dio el compuesto del título(40 mg) en forma de un sólido blanco. δ H (CDCl₃, 400MHz): 1,21 (3H, t), 1,45 (6H, d), 2,85 (2H, t), 4,13 (2H, q), 4,51 (2H, t), 4,71 (1H, septete), 6,60 (1H, d), 7,07 (1H, d), 7,21 (1H, d), 7,45 (1H, d), 8,02 (1H, d), 8,08 (1H, d), 8,27 (1H, s), 8,47 (1H, s). MS (ES): C₂₄H₂₄ClN₃O₄ requiere 453; encontrado 454 (MH⁺).

Descripción para D7

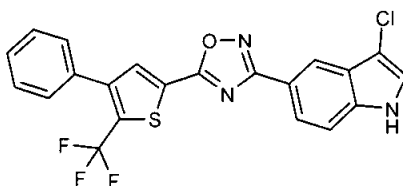
3-Cloro-5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol (D7)



D5 (300 mg) y NCS (113 mg) se disolvieron en DCM (4,2 ml) y se agitaron durante una noche a temperatura ambiente. Después, la mezcla de reacción se diluyó con DCM y se lavó con H₂O. La solución acuosa se extrajo con dos porciones adicionales de DCM y las disoluciones orgánicas combinadas se evaporaron hasta sequedad. El producto bruto se trituró con metanol para dar el compuesto del título (42 mg) en forma de un sólido pardo. Después se evaporó el metanol y el sólido pardo resultante se trituró con DCM para dar un segundo lote del compuesto del título (205 mg) en forma de un sólido pardo. δ H (d₆-DMSO, 400MHz): 1,37 (6H, d), 4,89 (1H, septete), 7,45 (1H, d), 7,62 (1H, d), 7,70 (1H, s), 7,93 (1H, d), 8,15 (1H, d), 8,24 (1H, s), 8,25 (1H, s), 11,77 (1H, s). MS (ES): C₁₉H₁₅³⁵Cl₂N₃O₂ requiere 387; encontrado 388 (MH⁺).

15 Descripción para D8

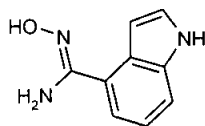
3-Cloro-5-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol (D8)



D2 (200 mg) y NCS (65 mg) se disolvieron en DCM (5 ml) y se agitaron durante una noche a temperatura ambiente. Después, la mezcla de reacción se repartió entre DCM y H₂O. La solución en DCM se evaporó hasta sequedad y se purificó sobre un cartucho de sílice Biotage, eluyendo con una mezcla del 25 al 75% de dietil éter en hexano. Esto dio el compuesto del título (36 mg) en forma de un sólido pardo. También se obtuvo un segundo lote del compuesto del título a partir de esta purificación (86 mg) en forma de un sólido pardo. δ H (CDCl₃, 400MHz): 7,28 (1H, m), 7,45-7,54 (6H, m), 7,93 (1H, s), 8,05 (1H, d), 8,28 (1H, s ancho), 8,49 (1H, s). MS (ES): C₂₁H₁₁ClF₃N₃OS requiere 445; encontrado 444 (M-H⁺).

Descripción 9

30 N-Hidroxi-1H-indol-4-carboximidamida (D9)

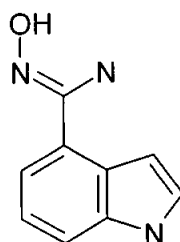


- 4-Cianoindol (850 mg) se disolvió en EtOH (25 ml). A esta solución, se añadió NaHCO₃ (2,51 g) y NH₂OH.HCl (831 mg). La mezcla se calentó a 70 °C y se agitó durante una noche. La reacción era incompleta, así que se calentó a 80 °C durante 5 otras 4 horas. La mezcla de reacción se filtró y evaporó para dar el compuesto del título (980 mg) en forma de un semisólido amarillo. No se intentó purificar.

Descripción para D9 (Procedimiento alternativo)

***N*-Hidroxi-1*H*-indol-4-carboximidamida (D9)**

10

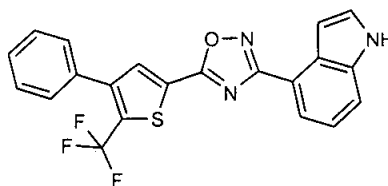


- 15 Una mezcla de 4-cianoindol (5,0g, 35,2 mmol), hidrógeno-carbonato de sodio (8,9g, 105,6 mmol) e hidrocloreuro de hidroxilamina (4,9g, 70,4 mmol) en etanol (200ml) se calentó a 55 °C durante una noche. Se añadieron hidrógeno-carbonato de sodio (5,9g, 70 mmol) e hidrocloreuro de hidroxilamina (4,9g, 70,4 mmol). La mezcla se calentó durante 4 días hasta que sólo una pequeña cantidad de material de partida
- 20 estaba presente. Los materiales inorgánicos se separaron por filtración, lavando bien el sólido con etanol y el disolvente se separó por evaporación. El residuo se trituro con dietil éter para dar 5,8g de un sólido blanquecino. δ H (400 MHz, metanol-d₄) 6,76-6,78 (1H, m), 7,12 (1H, t), 7,24 (1H, dd), 7,29-7,33 (1H, m) 7,46 (1H, dd).

25 **Descripción para D10**

4-{5-[4-Fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1*H*-indol (D10)

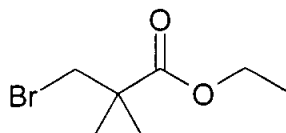
10/



Ácido 4-fenil-5-(trifluorometil)-2-tiofenocarboxílico (310 mg), HOBT (170 mg) y EDCI.HCl (242 mg) se disolvieron en DMF (3 ml) y agitaron a temperatura ambiente 20 min. **D9** (200 mg) se disolvió en DMF (3 ml) y se añadió a la solución anterior y se continuó agitando a temperatura ambiente durante dos horas. Después, la mezcla de reacción se calentó a 90 °C, se enfrió a RT, se dejó estar durante una noche, se volvió a calentar a 80 °C y se agitó durante 3 horas, se enfrió a temperatura ambiente y se evaporó hasta sequedad. El residuo se re-disolvió en H₂O y extrajo con EtOAc (x 3) y los extractos orgánicos combinados se evaporaron hasta sequedad. El residuo se purificó por cromatografía instantánea sobre sílice, eluyendo con una mezcla del 25 al 75% de dietil éter en hexano para dar el compuesto del título (265 mg) en forma de un sólido pardo. Una muestra de este compuesto (100 mg) se purificó por MDAP para dar el compuesto del título (62 mg) en forma de un sólido blanquecino. δ H (CDCl₃, 400MHz): 7,33-7,36 (2H, m), 7,41-7,42 (1H, m), 7,46-7,52 (5H, m), 7,61 (1H, d), 7,94 (1H, s), 8,06 (1H, d), 8,46 (1H, s ancho). MS (ES): C₂₁H₁₂F₃N₃OS requiere 411; encontrado 412 (MH⁺).

Descripción para D11

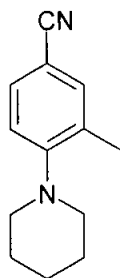
3-Bromo-2,2-dimetilpropanoato de etilo (D11)



Ácido 3-bromo-2,2-dimetilpropanoico (200 mg) se disolvió en EtOH (5 ml) y se trató con H₂SO₄ concentrado (0,4 ml). Esta mezcla se calentó a reflujo durante una noche y después se evaporó. El residuo se extrajo del H₂O con EtOAc (x 2) y las disoluciones orgánicas combinadas se secaron y evaporaron para dar el compuesto del título (316 mg) como un aceite claro. δ H (CDCl₃, 400MHz) 1,20 (3H, t), 1,32 (6H, s), 3,51 (2H, s), 4,18 (2H, q).

Descripción para D12

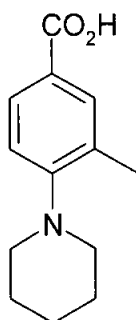
3-Etil-4-(1-piperidinil)benzonitrilo (D12)



4-Amino-3-etilbenzonitrilo (3,0 g, 20,5 mmol), 1,5-dibromopentano (11,1 mL, 82,1 mmol), carbonato de potasio (5,67 g, 41,0 mmol) y agua (39,6 mL) se repartieron todos por igual entre diez viales para microondas y cada uno de ellos se calentó a 160 °C durante 1 h. Todas las mezclas de reacción se combinaron y extrajeron dos veces con acetato de etilo (40 mL) y las fracciones orgánicas combinadas se secaron (separador de fases) y concentró a vacío. Se añadió diclorometano y después la mezcla se filtró antes de purificar el filtrado por cromatografía sobre sílice, eluyendo con acetato de etilo 2-5 % en hexano para dar el compuesto del título en forma de un aceite incoloro (823 mg, 3,85 mmol). El análisis indicó que el compuesto contenía una pequeña impureza de dibromopentano. δ H (metanol- d_4 , 400 MHz) 7,52 (1H, dd), 7,47 (1H, dd), 7,13 (1H, d), 2,89 (4H, dd), 2,71 (2H, q), 1,76-1,71 (4H, m), 1,64-1,56 (2H, m), 1,25 (3H, t). MS (ES): $C_{14}H_{18}N_2$ requiere 214; encontrado 215 (MH^+).

Descripción para D13

Ácido 3-etil-4-(1-piperidinil)benzoico (D13)

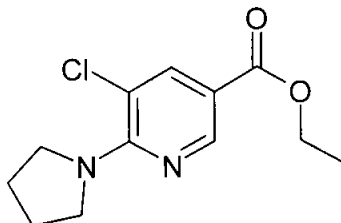


3-Etil-4-(1-piperidinil)benzonitrilo (**D12**) (817 mg, 3,82 mmol) e hidróxido de potasio (2,14 g, 38,2 mmol) en etanol (35 mL) y agua (8 mL) se calentaron a 90 °C (temperatura de bloqueo) durante 9 h. Se añadió más hidróxido de potasio (2,14 g, 38,2 mmol) y agua (8 mL) y la reacción se calentó durante otras 18 h. La reacción se dejó enfriar y se neutralizó con HCl acuoso. Por filtración, se recogió un sólido blanco y se intentó purificar el filtrado con un cartucho SCX, pero no se logró. Se

combinaron el sólido y el producto de la SCX, se añadió metanol y después la mezcla se aciduló con ácido acético. La mezcla se filtró para obtener el filtrado, que después se atrapó en un cartucho SCX, se lavó con metanol y eluyó con amoniaco 2M en metanol. A escala de ensayo, esto dio el compuesto del título en forma de un sólido blanco (96 mg, 0,41 mmol) y el material residual dio un aceite incoloro (563 mg, 2,41 mmol). δ H (metanol- d_4 , 400 MHz): 7,85 (1H, d), 7,74 (1H, dd), 7,03 (1H, d), 2,85 (4H, dd), 2,73 (2H, q), 1,72 (4H, m), 1,61 (2H, m), 1,25 (3H, t) ppm. MS (ES): $C_{14}H_{19}NO_2$ requiere 233; encontrado 234 (MH^+).

10 **Descripción para D14**

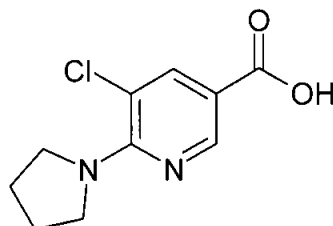
5-Cloro-6-(1-pirrolidinil)-3-piridincarboxilato de etilo (D14)



15 Una mezcla de éster etílico de ácido 5,6-dicloronicotínico (1,00 g, 4,57 mmol), pirrolidina (325 mg, 4,57 mmol), carbonato de potasio (632 mg, 4,57 mmol) y cobre en polvo (34 mg) en DMF (6,8 mL) se calentó a 130 °C en el microondas durante 20 min. Se añadió más pirrolidina (163 mg, 2,29 mmol) y la reacción se calentó a 130 °C durante 20 min. Se añadió agua (7 mL) y la mezcla se extrajo con acetato de etilo (2 x 14 mL). Los extractos orgánicos combinados se lavaron con agua (7 mL) y salmuera (7mL) antes de secarse (separador de fases) y concentrarse a vacío para dar el compuesto del título en forma de un aceite anaranjado (1,06 g, 4,17 mmol). δ H (metanol- d_4 , 400 MHz): 8,45 (1H, d), 7,98 (1H, d), 4,31 (2H, q), 3,82-3,75 (4H, m), 2,0-1,93 (4H, m), 1,36 (3H, t) ppm. MS (ES): $C_{12}H_{15}ClN_2O_2$ requiere 254, 256; encontrado 255, 257 (MH^+).

Descripción para D15

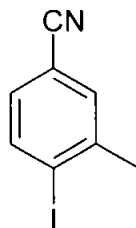
Ácido 5-cloro-6-(1-pirrolidinil)-3-piridincarboxílico (D15)



5-cloro-6-(1-pirrolidinil)-3-piridinacarboxilato de etilo (**D14**) (1,06 g, 4,16 mmol) en etanol (20 mL) e hidróxido de sodio acuoso (2M, 2,08 mL, 4,16 mmol) se calentó a 40 °C durante 18 h. La mezcla de reacción se dejó enfriar y se neutralizó con 2M HCl (aq.). El compuesto del título se obtuvo en forma de un sólido blanco y se separó por filtración y se lavó con metanol para dar el compuesto del título (243 mg, 1,08 mmol) SJ108923-113A3. El filtrado se atrapó en una columna SCX, eluyendo con amoníaco 2M en metanol para dar más compuesto del título como un sólido anaranjado (467 mg, 2,07 mmol). δ H (metanol- d_4 , 400 MHz): 8,55 (1H, d), 8,03 (1H, d), 3,76-3,70 (4H, m), 1,96-1,90 (4H, m). MS (ES): $C_{10}H_{11}ClN_2O_2$ requiere 226, 228; encontrado 227, 229 (MH^+).

Descripción para D16

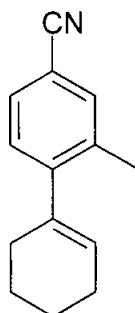
3-Etil-4-yodobenzonitrilo (D16)



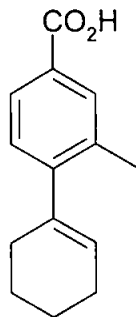
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A 4-amino-3-etilbenzonitrilo (2,50 g, 17,1 mmol) agitado en agua (14 mL) a 0 °C se añadió ácido clorhídrico concentrado (7,80 mL, 257 mmol) gota a gota seguido de una disolución de nitrito de sodio (1,24 g, 18,0 mmol) en agua (3,43 mL) gota a gota. La mezcla resultante se agitó durante 15 minutos y después se añadió a lo largo de 15 minutos a una disolución de yoduro de potasio (2,98 g, 18,0 mmol) en agua (6,0 mL) a 0 °C. La mezcla se agitó a temperatura ambiente durante 2 h. La mezcla se extrajo con acetato de etilo (3 x 100 mL) y las fracciones orgánicas combinadas se lavaron con salmuera (100 mL), se secaron (separador de fases) y concentraron a vacío para dar el compuesto del título en forma de un sólido pardo (4,21 g, 16,4 mmol). δ H (metanol- d_4 , 400 MHz): 8,02 (1H, d), 7,61 (1H, d), 7,24 (1H, dd), 2,80 (2H, q), 1,21 (3H, t). MS (ES): No se observaron iones de masas

25

Descripción para D17**4-(1-Ciclohexen-1-il)-3-etilbenzonitrilo (D17)**

- 5 Una mezcla de 3-etil-4-yodobenzonitrilo (**D16**) (1,23 g, 4,80 mmol), ácido 1-ciclohexen-1-ilborónico (907 mg, 7,20 mmol), metóxido de sodio (778 mg, 14,4 mmol) y cloruro de bis(trifenilfosfina)paladio (II) (337 mg, 0,48 mmol) en metanol anhidro (12 mL) se calentó a 80 °C durante 10 minutos en el microondas. La mezcla de reacción se repartió entre acetato de etilo (40 mL) y agua (40 mL) antes de lavar
- 10 adicionalmente la capa orgánica con agua (40 mL), se secó (separador de fases) y se concentró *a vacío*. El material bruto se purificó por cromatografía sobre sílice, eluyendo con 0-5 % de EtOAc en hexano a lo largo de 30 minutos para dar el compuesto del título en forma de un aceite amarillo (824 mg, 3,91 mmol). δ H (metanol- d_4 , 400 MHz) 7,56 (1H, d), 7,46 (1H, dd), 7,19 (1H, d), 5,61-5,56 (1H, m),
- 15 2,68 (2H, cuart), 2,23-2,16 (4H, m), 1,85-1,68 (4H, m), 1,20 (3H, t). MS (ES): No se observaron iones de masas

Descripción para D18**4-(1-Ciclohexen-1-il)-3-etilbenzonitrilo (D18)**

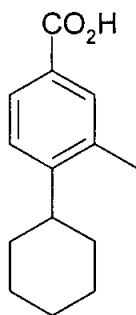
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4-(1-ciclohexen-1-il)-3-etilbenzonitrilo (**D17**) (824 mg, 3,91 mmol) e hidróxido de potasio (2,19 g, 39,1 mmol) en etanol (36 mL) y agua (8 mL) se calentaron a 90 °C (temperatura de bloqueo) durante 20 h. La mezcla de reacción se concentró *a vacío*

y el residuo se repartió entre acetato de etilo (120 mL) y ácido clorhídrico acuoso (2M, 50 mL) antes de lavar la fase orgánica con más ácido clorhídrico (2M, 50 mL), secar (separador de fases) y concentrar *a vacío* para dar el compuesto del título en forma de un aceite amarillo (808 mg, 3,51 mmol). δ H (metanol- d_4 , 400 MHz) 7,87 (1H d), 7,76 (1H dd), 7,11 (1H, d) 5,59-5,54 (1H, m), 2,68 (2H, q), 2,25-2,15 (4H, m), 1,84-1,67 (4H, m), 1,20 (3H, t). LCMS (ES): $C_{15}H_{18}O_2$ requiere 230; encontrado 229 ($M-H^+$).

Descripción para D19

10 **Ácido 4-ciclohexil-3-etilbenzoico (D19)**

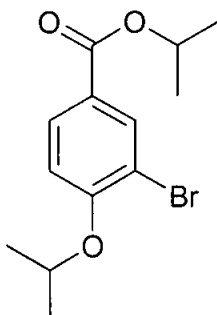


Ácido 4-(1-ciclohexen-1-il)-3-etilbenzoico (**D18**) (803 mg, 3,49 mmol) se disolvió en metanol (70 mL) y se hidrogenó en una H-Cuba usando un cartucho de paladio sobre carbono. La disolución del producto se concentró *a vacío* para dar el compuesto del título en forma de un sólido blanco (792 mg, 3,41 mmol). δ H (metanol- d_4 , 400 MHz): 7,82-7,68 (2H, m), 7,33 (1H, d), 2,83 (1H, m), 2,73 (2H, q), 1,87 (2H, m), 1,85-1,70 (3H, m), 1,58-1,30 (5H, m), 1,22 (3H, t). LCMS (ES): No se observaron iones de masas

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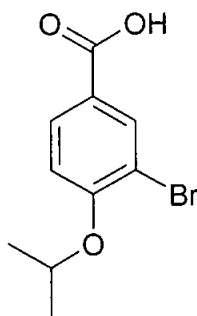
Descripción para D20

3-bromo-4-[(1-metiletil)oxi]benzoato de 1-metiletilo (D20)



Una mezcla de ácido 3-bromo-4-hidroxibenzoico (2,00 g, 9,22 mmol), 2-yodopropano (1,85 mL, 18,4 mmol) y carbonato de potasio (2,55 g, 18,4 mmol) en DMF (175 mL) se calentó a reflujo durante 5 h. La reacción se dejó enfriar y se filtró. El filtrado se concentró *a vacío* y el residuo se repartió entre acetato de etilo (150 mL) y agua (150 mL), que se alcalinizó con NaOH 2M. La fase orgánica se secó (separador de fases) y concentró *a vacío* para dar el compuesto del título en forma de un aceite amarillo (2,36 g, 7,84 mmol). δ H (metanol- d_4 , 400 MHz): 8,05 (1H, d), 7,90 (1H, dd), 7,25 (1H, d), 5,10 (1H, septete), 4,81 (1H, septete), 1,32 (6H, d), 1,31 (6H, d) ppm. MS (ES): No se observaron iones de masas

10

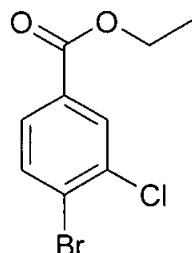
Descripción para D21**Ácido 3-bromo-4-[(1-metiletil)oxi]benzoico (D21)**

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Una solución de 3-bromo-4-[(1-metiletil)oxi]benzoato de 1-metiletilo (D20) (2,36 g, 7,84 mmol) en etanol (100 mL) e hidróxido de sodio acuoso (2M, 39 mL) se calentó a reflujo durante 5 h. La mezcla de reacción se concentró *a vacío* y se repartió entre acetato de etilo (125 mL) y agua (125 mL), esta última se aciduló con 2M HCl (40 mL). La capa acuosa se extrajo con más acetato de etilo (70 mL) y los extractos orgánicos combinados se secaron (separador de fases) y concentraron *a vacío* para dar el compuesto del título en forma de un sólido blanquecino (1,83 g, 7,06 mmol). δ H (metanol- d_4 , 400 MHz): 8,05 (1H, d), 7,89 (1H, dd), 7,23 (1H, d), 4,79 (1H, septete), 1,32 (6H, d). MS (ES): $C_{10}H_{11}BrO_3$ requiere 258, 260; encontrado 257, 259 (M-H⁺).

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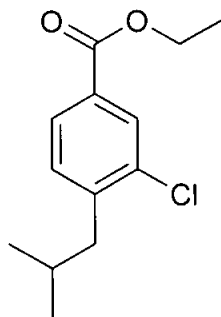
Descripción para D22**4-Bromo-3-clorobenzoato de etilo (D22)**



A una suspensión de ácido 4-bromo-3-clorobenzoico (5,00 g, 21,2 mmol) en etanol (50 mL) se añadió ácido sulfúrico (5 mL) y la mezcla resultante se calentó a reflujo durante 60 h. La reacción se repartió entre acetato de etilo (50 mL) y agua (50 mL). La capa acuosa se extrajo con más acetato de etilo (mL) y las fracciones orgánicas combinadas se secaron (separador de fases) y concentraron *a vacío* para dar el compuesto del título en forma de un aceite/sólido blanquecino (5,09 g, 19,3 mmol). δ H (d_6 -DMSO, 400 MHz): 8,06 (1H, d), 7,96 (1H, d), 7,80 (1H, dd), 4,33 (2H, q), 1,33 (3H, t). MS (ES): No se observaron iones de masas

Descripción para D23

3-Cloro-4-(2-metilpropil)benzoato de etilo (D23)

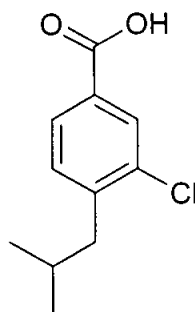


Una solución de bromuro de isobutil zinc en THF (0,5 M, 30 mL, 15,0 mmol) se añadió bajo argón a 4-bromo-3-clorobenzoato de etilo (**D22**) (2,00 g, 7,60 mmol) y después se añadió complejo de dicloruro de 1,1'-bis(difenilfosfino)ferrocenopaldio(II) con diclorometano (930 mg, 1,14 mmol). La reacción se calentó a reflujo durante 4,5 h. La mezcla se concentró a vacío y el residuo se repartió entre acetato de etilo (125 ml) y agua (125 ml). Se formó un sólido, que se separó por filtración y se descartó. La capa orgánica se lavó con agua (100 mL), se secó (separador de fases) y concentró *a vacío*. El producto bruto se purificó por cromatografía sobre sílice, eluyendo con 0-5 % EtOAc en hexano a lo largo de 30 minutos para dar el compuesto del título en forma de un aceite incoloro (1,76 g, 7,33 mmol). δ H (d_6 -DMSO, 400 MHz): 7,91 (1H,d), 7,80 (1H, dd), 7,46 (1H, d), 4,30 (2H, q), 2,66 (2H, d),

1,88-2,01 (1H, m), 1,32 (3H, t), 0,89 (6H, d). MS (ES): No se observaron iones de masas

Descripción para D24

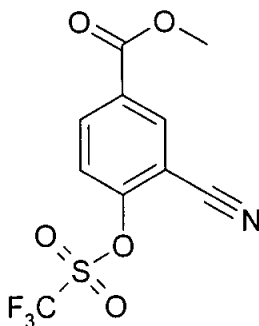
5 **Ácido 3-cloro-4-(2-metilpropil)benzoic(D24)**



Una solución de 3-cloro-4-(2-metilpropil)benzoato de etilo (**D23**) (1,76 g, 7,33 mmol), e hidróxido de sodio acuoso (2M, 3,70 mL, 7,4 mmol) en etanol (30 mL) se calentó a 40 °C durante 3 h. La mezcla de reacción se concentró *a vacío* y el residuo se repartió entre acetato de etilo (100 mL) y agua (100 mL), esta última se aciduló con 2M HCl (4 mL). La capa acuosa se extrajo con acetato de etilo (100 mL) y los extractos orgánicos combinados se secaron (separador de fases) y concentraron *a vacío* para dar el compuesto del título en forma de un sólido blanco (1,35 g, 6,36 mmol). δ H (d_6 -DMSO, 400 MHz): 13,20 (1H, s ancho), 7,89 (1H, d), 7,82 (1H, dd), 7,44 (1H, d), 2,64 (2H, d), 1,94 (1H, m), 0,89 (6H, d). MS (ES): $C_{11}H_{13}^{35}ClO_2$ requiere 212; encontrado 211 (M-H⁺).

Descripción para D25

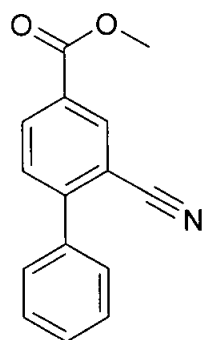
20 **3-Ciano-4-[[[(trifluorometil)sulfonil]oxi]benzoato de metilo (D25)**



A una disolución de 3-ciano-4-hidroxibenzoato de metilo (3 g, 16,93 mmol) y trietilamina (3,54 ml, 25,4 mmol) en diclorometano seco (60 ml) a 0 °C bajo una corriente de argón se añadió anhídrido trifluorometanosulfónico (3,15 ml, 18,63 mmol) lentamente gota a gota. La reacción se dejó calentar a temperatura ambiente y se agitó durante 1 h. La mezcla de reacción se lavó con carbonato de potasio acuoso al 10% (2 x 50 mL) y después HCl acuoso (2M, 2 x 50 mL) antes de secar la fase orgánica (separador de fases) y separar el disolvente *a vacío* para dar el compuesto del título en forma de un aceite pardo oscuro, (5,165 g, 16,70 mmol). δ H (CDCl₃, 400 MHz): 8,44 (1H, d), 8,38 (1H, dd), 7,60 (1H, d), 3,99 (3H, s). MS (ES): No se observaron iones de masas

Descripción para D26

2-Ciano-4-bifenilcarboxilato de metilo (D26)

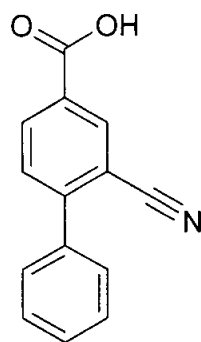


La siguiente reacción se repartió entre dos lotes con la mitad de las cantidades: 3-Ciano-4-[[trifluorometil]sulfonil]oxi]benzoato de metilo (**D25**) (1,5 g, 4,85 mmol), ácido fenilborónico (1,183 g, 9,70 mmol), carbonato de potasio (2,011 g, 14,55 mmol) y tetrakis(trifenil)fosfina paladio(0) (0,561 g, 0,485 mmol) se recogieron en DMF (24 ml) y la mezcla se calentó en el microondas durante 30 min a 150 °C. Las dos reacciones se combinaron y diluyeron con acetato de etilo (50 mL) y la mezcla se filtró a través de tierra de diatomeas para separar las trazas de paladio. El filtrado se concentró *a vacío* para disminuir la cantidad de DMF y después el residuo se repartió entre bicarbonato de sodio acuoso saturado (50 mL) y acetato de etilo (50 mL). La fase orgánica se lavó con más bicarbonato de sodio (50 mL) y después agua (50 mL) antes de secarla (MgSO₄), filtrar y separar el disolvente *a vacío*. El sólido pardo se purificó por cromatografía sobre sílice, eluyendo con 0-25 % de EtOAc en isohexano a lo largo de 35 minutos para dar el compuesto del título en forma de un sólido blanco (935 mg, 3,94 mmol). δ H (d₆-DMSO, 400 MHz): 8,42 (1H,

d), 8,29 (1H, dd), 7,81 (1H, d), 7,65 (2H, m), 7,60 -7,50 (3H, m), 3,92 (3H, s). MS (ES): No se observaron iones de masas

Descripción para D27

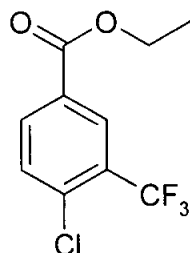
5 **Ácido 2-ciano-4-bifenilcarboxílico (D27)**



A 2-ciano-4-bifenilcarboxilato de metilo (**D26**) (935 mg, 3,94 mmol) se añadió etanol (18 ml) pero no se producía la disolución, así que se añadió diclorometano (10 ml). Después se añadió hidróxido de sodio (2 ml, 4,00 mmol) y la reacción se agitó durante 2 h. A la mezcla se añadió diclorometano (20 mL) y HCl acuoso 2M 10 mL). Las capas se separaron y la capa acuosa se extrajo con más diclorometano (20 ml). La fase orgánica combinada se secó (separador de fases) y el disolvente se separó *a vacío* para dar un sólido blanco, que se disolvió en metanol (30 mL) y se añadió hidróxido de sodio acuoso (2M, 3 mL). La reacción se agitó a temperatura ambiente durante 1 h antes de la adición de agua (20 mL). La mezcla de reacción se agitó durante 1 h más. Se añadió diclorometano (60 mL) y la mezcla se sacudió y se separaron las capas. La fase acuosa se extrajo con más diclorometano (50 mL) antes de secar la fase orgánica combinada (separador de fases) y separar el disolvente *a vacío* para dar el compuesto del título en forma de un sólido blanco, (849 mg, 3,80 mmol). δ H (d_6 -DMSO, 400 MHz): 13,60 (1H, s ancho), 8,38 (1H, d), 8,28 (1H, dd), 7,78 (1H, d), 7,63 (2H, m), 7,60-7,50 (3H, m). MS (ES): $C_{14}H_9NO_2$ requiere 223; encontrado 222 (M-H⁺).

Descripción para D28

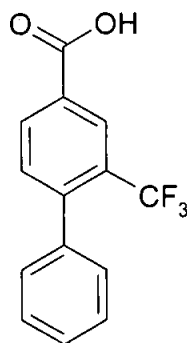
25 **4-Cloro-3-(trifluorometil)benzoato de etilo (D28)**



Ácido 4-cloro-3-(trifluorometil)benzoico (1 g, 4,45 mmol) se disolvió en etanol (3 ml) y se añadió ácido sulfúrico concentrado (0,15 ml). La mezcla se calentó en el microondas at 100 °C durante 5 minutos y después 120 °C durante 15 minutos. El disolvente se separó a vacío y el residuo se repartió entre bicarbonato de sodio acuoso saturado (50 ml) y acetato de etilo (50 ml). La capa acuosa se extrajo con más EtOAc (50 ml) y las fases orgánicas se combinaron, se secaron con un separador de fases y concentraron a vacío para dar el compuesto del título (1,026 g) (DN108121-148A3) en forma de un aceite incoloro. δ H (metanol- d_4 , 400 MHz) 1,40 (3H, t), 4,41 (2H, q), 7,76 (1H, d), 8,21 (1H, dd), 8,33 (1H, d). MS (ES) no se observaron iones de masas.

Descripción para D29

Ácido 2-(trifluorometil)-4-bifenilcarboxílico (D29)



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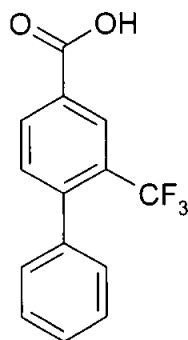
La reacción se dividió en 4, usando la cuarta parte de los reactivos en cada caso: a una mezcla de 4-bromo-3-(trifluorometil)benzonitrilo (4 g, 16,00 mmol), ácido fenilborónico (3,90 g, 32,0 mmol) y carbonato de potasio (6,63 g, 48,0 mmol) en N,N-dimetilformamida (DMF) (64 ml) se añadió tetrakis(trifenilfosfina) paladio(0) (1,849 g, 1,600 mmol). Cada reacción se calentó en el microondas a 150 °C durante 30 min. Las mezclas de reacción combinadas se filtraron a través de celite, se lavaron con acetato de etilo y se separó el disolvente a vacío. El residuo se repartió entre acetato de etilo (100 mL) y agua (100 mL) y la fase orgánica se lavó con disolución de bicarbonato de sodio (100 mL). La fase orgánica se secó ($MgSO_4$), filtró y se

20

separó el disolvente a vacío. El aceite pardo se trituro con diclorometano y filtró para dar un sólido amarillo pálido, 2-(trifluorometil)-4-bifenilcarboxamida (2,47 g) que se usó sin más purificación. A 2-(trifluorometil)-4-bifenilcarboxamida (2 g, 7,54 mmol) en etanol (80 ml) se añadió hidróxido de potasio (4,23 g, 75 mmol) y agua y la
5 mezcla se calentó a 90 °C durante 18 h. La mezcla de reacción se concentró a vacío y el residuo se repartió entre diclorometano (100 mL) y 2M HCl (100 mL). La fase orgánica se aisló y se secó (separador de fases) y el disolvente se separó a vacío para dar el producto bruto. La purificación usando el cartucho en fase inversa Biotage Horizon, eluyendo con 5-100 % de MeCN en agua dio un sólido
10 blanquecino, el compuesto del título (960 mg) (N2123-46-A5). MS (ES): $C_{14}H_9F_3O_2$ requiere 266; encontrado 265 ($M-H^+$).

Descripción para D29 (Procedimiento alternativo)

Ácido 2-(trifluorometil)-4-bifenilcarboxílico (D29)



15

Lote A: Una mezcla de **D98** (1,0 g, 3,96 mmol), ácido fenilborónico (724 mg, 5,94 mmol), acetato de paladio (44 mg), (diciclohexilfosfino)bifenilo (140,2 mg) y fluoruro de potasio (689 mg, 11,9 mmol) en THF (8 ml) se calentó en el microondas at 120 °C durante un total de 40 minutos.

20 Lote B: Una mezcla de **D28** (500 mg, 1,98 mmol), ácido fenilborónico (290 mg, 2,38 mmol), acetato de paladio (2,2 mg), (diciclohexilfosfino)bifenilo (7 mg) y fluoruro de potasio (344 mg, 5,8 mmol) en THF (4 ml) se calentó en el microondas at 120 °C durante 20 minutos.

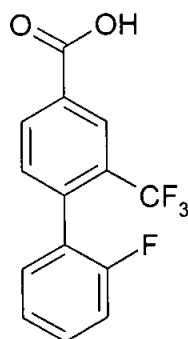
Las mezclas de reacción de los lotes A & B se combinaron, filtraron y el filtrado se
25 concentró a vacío. El residuo se purificó por cromatografía instantánea (0 a 5% de EtOAc en hexano para dar una mezcla de material de partida y producto acoplado. Este material se disolvió en etanol (10 ml) y NaOH 2M (aq) (5ml) y después se calentó a reflujo durante 3 h. El disolvente se separó a vacío y el residuo se repartió entre DCM y 2M aq. HCl. La capa acuosa se extrajo con más DCM. Las fases

orgánicas se combinaron y se concentraron al vacío. The material bruto se purificó por cromatografía en fase reversa sobre Horizon eluyendo con 5 a 100% MeCN en agua para dar el compuesto del título en forma de un sólido blanco (367 mg) . δ H (d₆-DMSO, 400 MHz) 7,31-7,40 (2H, m), 7,44-7,52 (3H, m), 7,57 (1H, d), 8,24 (1H, dd), 8,29 (1H, d), 13,57 (1H, s ancho). MS (ES): C₁₄H₉F₃O₂ requiere 266; encontrado 265 (M-H⁺).

Descripción para D30

Ácido 2'-Fluoro-2-(trifluorometil)-4-bifenilcarboxílico (D30)

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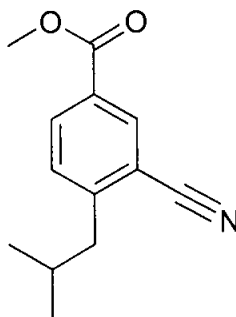


Este material se preparó usando un método similar al descrito para **D29** usando ácido (2-fluorofenil)borónico y **D98** excepto que sólo se realizó una reacción de acoplamiento, similar al lote A y la reacción de acoplamiento se calentó durante 20 minutos. MS (ES): C₁₄H₈F₄O₂ requiere 284; encontrado 283 (M-H⁺).

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Descripción para D31

3-Ciano-4-(2-metilpropil)benzoato de metilo (D31)



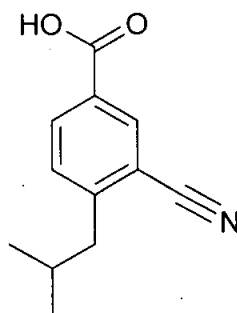
20 A 3-ciano-4-[[trifluorometil)sulfonil]oxi]benzoato de metilo (**D25**) (1,5 g, 4,85 mmol) se añadió bromo(2-metilpropil)zinc (48,5 ml, 24,25 mmol) en tetrahidrofurano (50 ml) bajo argón. A la disolución se añadió después complejo de 1,1'-bis(difenilfosfino)ferrocenodichloro paladio(II) con diclorometano (0,355 g, 0,485

mmol) y la reacción se calentó a reflujo durante 6 h. La mezcla se inactivó con agua (2 mL) y después se filtró a través de celite, lavando con acetato de etilo. El disolvente se retiró al vacío. El residuo se repartió entre acetato de etilo (50 mL) y agua (50 mL) y la fase orgánica se secó (separador de fases) y se separó el disolvente *a vacío*. El residuo se purificó por cromatografía sobre sílice, eluyendo con 0-15 % de EtOAc en iso-hexano a lo largo de 40 min. Se recogieron dos lotes, uno de los cuales era el compuesto del título en forma de un aceite incoloro (233 mg, 1,072 mmol). δ H (CDCl₃, 400 MHz): 8,28 (1H, d), 8,15 (1H, dd), 7,38 (1H, d), 3,94, 3H, s), 2,78 (2H, d), 2,02 (1H, m), 0,96 (6H, d).

10

Descripción para D32

Ácido 3-Ciano-4-(2-metilpropil)benzoico(D32)



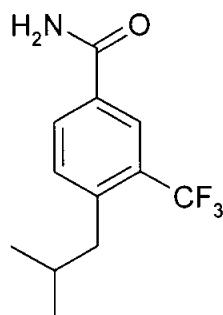
3-ciano-4-(2-metilpropil)benzoato de metilo (D31) (233 mg, 1,072 mmol) se disolvió en etanol (4 ml) y se añadió hidróxido de sodio acuoso 2M (1 ml, 2 mmol). La reacción se agitó durante 1 h. Se añadió HCl acuoso 2M (10 mL) y la mezcla extrajo con diclorometano (20 mL + 10 mL). Las fases orgánicas se aislaron y se secaron con el separador de fases y se combinaron antes de separar el disolvente *a vacío* para dar el compuesto del título en forma de un sólido blanco (203 mg, 0,999 mmol). δ H (d₆-DMSO, 400 MHz) 13,43 (1H, s ancho), 8,29 (1H, d), 8,14 (1H, dd), 7,59 (1H, d), 2,74 (2H, d), 1,96 (1H, m), 0,91 (6H, d). MS (ES): C₁₂H₁₃NO₂ requiere 203; encontrado 202 (M-H⁺).

20

Descripción para D33

4-(2-Metilpropil)-3-(trifluorometil)benzamida (D33)

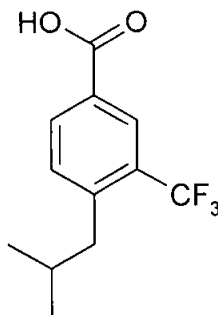
25



A una disolución de 4-bromo-3-trifluorometilbenzonitrilo (1,25 g, 5,0 mmol) y bromuro de isobutil zinc (25 mmol) en THF (50 mL, 25 mmol) bajo argón se añadió el complejo de 1,1'-bis(difenilfosfino)ferrocenedicloro paladio(II) con diclorometano (612 mg, 0,75 mmol) y la reacción se calentó a reflujo durante 5 h. La mezcla se concentró a vacío y el residuo se repartió entre acetato de etilo (80 mL) y agua (80 mL). Se formó un sólido y se separó por filtración y se descartó. La capa orgánica se lavó con agua (80 mL) antes de secarla (separador de fases) y concentrarla a vacío para dar el compuesto del título bruto como un aceite negro. Este se usó directamente en la siguiente etapa (1,35 g).

Descripción para D34

Ácido 4-(2-metilpropil)-3-(trifluorometil)benzoico (D34)

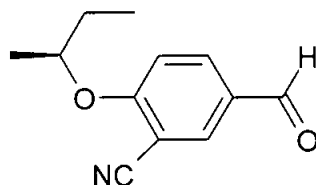


4-(2-metilpropil)-3-(trifluorometil)benzamida (**D33**) (1,35 g, 5,50 mmol) se disolvió junto con hidróxido de potasio (3,09 g, 55,0 mmol) en etanol (40 ml) y agua (10,0 ml) y la disolución se calentó a reflujo durante 18 h. La mezcla de reacción se concentró a vacío y la mezcla se separó entre EtOAc (150 mL) e hidróxido de sodio acuoso (2M, 150 mL). Las capas se separaron y la fase orgánica se extrajo con más disolución de hidróxido de sodio (200 ml). La LCMS de ambas fases indicó que había producto en ambas. Por lo tanto, la fase acuosa se aciduló a pH1 con HCl (5M) y se extrajo de nuevo en EtOAc (2 x 150 mL) y estas fases orgánicas se combinaron con la fase orgánica original. El disolvente se separó a vacío y el

residuo se purificó por cromatografía en fase inversa eluyendo con 5-100 % de MeCN en H₂O a lo largo de 2000 mL y se separó el disolvente a vacío para dar un sólido pardo (690 mg, 2,410 mmol). Este sólido se trituró con hexano para dar el compuesto del título como un sólido de color canela (135 mg, 0,548 mmol) y el filtrado se purificó por MDAP para dar más compuesto del título en forma de un sólido blanco (102 mg, 0,414 mmol). δ H (d₆-DMSO, 400 MHz): 13,39 (1H, s ancho), 8,16 (1H, s), 8,13 (1H, d), 7,62 (1H, d), 2,69 (2H, d), 1,97 (1H, m), 0,90 (6H, d). MS (ES): C₁₂H₁₃F₃O₂ requiere 246; encontrado 245 (M-H⁺).

10 **Descripción para D35**

5-Formil-2-[(1S)-1-metilpropil]oxi}benzonitrilo (D35)



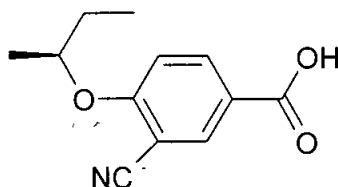
(2S)-2-Butanol (0,99 g, 0,013 mol) se disolvió en DMF (50 ml) y la disolución se enfrió a 0 °C. A esto se añadió hidruro de sodio, (dispersion al 60% en aceite mineral, 1,54g, 0,036 mol) en porciones, la mezcla se agitó a 0 °C durante 10 minutos una vez terminada la adición. Después se añadió 2-fluoro-5-formylbenzonitrilo (2,0 g, 0,013 mol) y la mezcla de reacción se dejó calentar a temperatura ambiente (lentamente dentro del baño de hielo) y la mezcla de reacción se agitó durante una noche a temperatura ambiente. Después, la mezcla de reacción se enfrió a 0 °C, se inactivó con salmuera y diluyó con EtOAc (~25ml). La mezcla se repartió y la fracción orgánica se extrajo con agua (~30ml), las fases orgánicas combinadas se secaron haciéndolas pasar a través de un cartucho separador de fases y después se evaporó hasta sequedad a presión reducida para dar el producto bruto. El residuo bruto se purificó en un cartucho 40+M Biotage, eluyendo con una mezcla del 20 al 50 % de EtOAc en hexano. Esto dio el compuesto del título(220 mg) en forma de un sólido blanco. δ H (d₆-DMSO, 400 MHz): 9,88 (1H, s), 8,30 (1H, s), 8,15 (1H, d), 7,49 (1H, d), 4,73-4,81 (1H, m), 1,63-1,79 (2H, m), 1,33 (3H, d), 0,95 (3H, t). MS (ES): C₁₂H₁₃NO₂ requiere 203; encontrado 204 (MH⁺).

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Descripción para D36

Ácido 3-ciano-4-[(1S)-1-metilpropil]oxi}benzoico (D36)

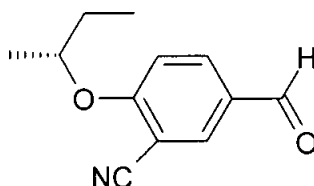
208



A una disolución de 5-formil-2-[[*(1S)*-1-metilpropil]oxi]benzonitrilo (**D35**) (220mg, 1,08 mmol) en ácido acético (20ml) se añadió perborato de sodio tetrahidratado (334mg, 2,17 mmol), la mezcla de reacción se calentó a 50 °C a lo largo del fin de semana. La mezcla de reacción se enfrió y se concentró al vacío. Se añadió agua (~50ml), se añadió EtOAc (~30ml) y se repartieron las capas, la capa acuosa se extrajo dos veces más con EtOAc (~30ml) y las fases orgánicas combinadas se evaporaron hasta sequedad a presión reducida para dar el compuesto del título (245mg) en forma de un sólido blanquecino. δ H (d_6 -DMSO, 400 MHz): 8,17 (2H, apparent d), 7,39 (1H, s), 4,68-4,74 (1H, m), 1,55-1,76 (2H, m), 1,31 (3H, d), 0,95 (3H, t). MS (ES): $C_{12}H_{13}NO_2$ requiere 219; encontrado 220 (MH^+).

Descripción para D37

5-Formil-2-[[*(1R)*-1-metilpropil]oxi]benzonitrilo (D37).

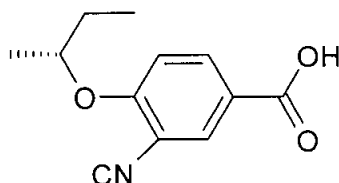


(2*R*)-2-Butanol (0,99 g, 0,013 mol) se disolvió en DMF (50 ml) y la disolución se enfrió a 0 °C. A esto se añadió hidruro de sodio, dispersion al 60% en aceite mineral (1,54g, 0,036 mol) en porciones, la mezcla se agitó a 0 °C durante 10 minutos una vez terminada la adición. Después se añadió 2-fluoro-5-formilbenzonitrilo (2,0 g, 0,013 mol) y la mezcla de reacción se dejó calentar a temperatura ambiente (lentamente dentro del baño de hielo) y la mezcla de reacción se agitó durante una noche a temperatura ambiente. Después, la mezcla de reacción se enfrió a 0 °C, se inactivó con salmuera y diluyó con EtOAc (~25ml). La mezcla se repartió y la fracción orgánica se extrajo con agua (~30ml), las fases orgánicas combinadas se secaron haciéndolas pasar a través de un cartucho separador de fases y se evaporó hasta sequedad a presión reducida para dar el producto bruto. El residuo bruto se purificó en un cartucho 40+M Biotage, eluyendo con una mezcla del 20 al 50 % de EtOAc en hexano. Esto dio el compuesto del título (310 mg) en forma de un aceite

amarillo. δH (d_6 -DMSO, 400 MHz): 9,88 (1H, s), 8,30 (1H, s), 8,15 (1H, d), 7,49 (1H, d), 4,73-4,81 (1H, m), 1,63-1,79 (2H, m), 1,33 (3H, d), 0,95 (3H, t) ppm.

Descripción para D38

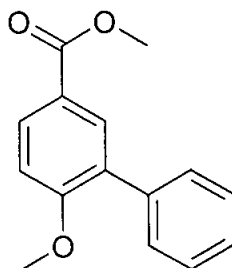
5 **Ácido 3-ciano-4-[(1R)-1-metilpropil]oxi}benzoico (D38)**



A una disolución de 5-formil-2-[(1R)-1-metilpropil]oxi}benzonitrilo (D37) (310mg, 1,53 mmol) en ácido acético (30ml) se añadió perborato de sodio tetrahidratado (471mg, 3,05 mmol), la mezcla de reacción se calentó a 50 °C a lo largo del fin de semana. La mezcla de reacción se concentró a vacío y se añadió agua (~50ml), se añadió EtOAc (~30ml) y se repartieron las capas, la capa acuosa se extrajo dos veces más con EtOAc (~30ml) y las fases orgánicas combinadas se evaporaron hasta sequedad a presión reducida para dar el compuesto del título (315 mg) en forma de un sólido blanquecino. δH (d_6 -DMSO, 400 MHz): 8,07-8,24 (2H, m), 7,38 (1H, d), 4,63-4,77 (1H, m), 1,55-1,83 (2H, m), 1,31 (3H, d), 0,95 (3H, t). EM (ES⁺): C₁₂H₁₃NO₂ requiere 219; encontrado 220 (MH⁺).

Descripción para D39

6-(Metiloxi)-3-bifenilcarboxilato de metilo (D39)



20

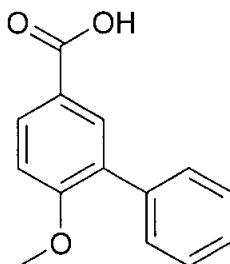
3-bromo-4-(metiloxi)benzoato de metilo (245 mg, 1 mmol, obtenibles en el mercado) se disolvió en DME : Na₂CO₃ 2N (2:1, 18 ml) y después se añadieron ácido fenilborónico (244 mg) y tetrakis(trifenil)fosfina paladio(0) (58 mg). La reacción se calentó a 80 °C y después se dejó enfriar a lo largo de un fin de semana. Se añadieron EtOAc y agua, las fases orgánicas se separaron, secaron y evaporaron para dar un chicle negro. La purificación por cromatografía instantánea proporcionó el compuesto del título (194 mg) en forma de chicle. δH (d_6 -DMSO, 400MHz) 3,83

25

(3H, s), 3,85 (3H, s), 7,24 (1H, d), 7,33-7,50 (5H, m), 7,83 (1H, d), 7,97 (1H, dd). MS (ES): $C_{15}H_{14}O_3$ requiere 242; encontrado 243 (MH^+).

Descripción para D40

5 **Ácido 6-(metiloxi)-3-bifenilcarboxílico (D40)**

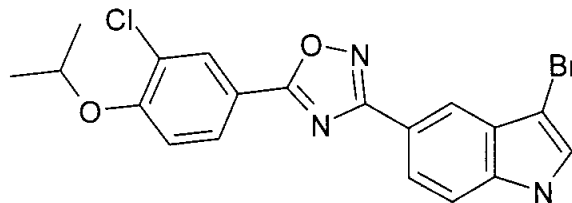


6-(metiloxi)-3-bifenilcarboxilato de metilo (**D39**) (194 mg, 0,8 mmol) se disolvió en NaOH 2N aq. (3 ml) y metanol (3 ml). Se agitó a temperatura ambiente durante una noche y después el disolvente orgánico se evaporó a vacío. Se añadieron EtOAc y agua, las fases orgánicas se separaron y después se aciduló la capa acuosa y se volvió a extraer. Los extractos orgánicos se secaron y evaporaron para dar 202 mg del compuesto del título en forma de un sólido blanco. δH (d_6 -DMSO, 400MHz) 3,84 (3H, s), 7,22 (1H, d), 7,33-7,49 (5H, m), 7,82 (1H, d), 7,95 (1H, dd), MS (ES^+): $C_{14}H_{12}O_3$ requiere 228; encontrado 229 ($M+H^+$).

15

Descripción para D41

3-Bromo-5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol (D41)

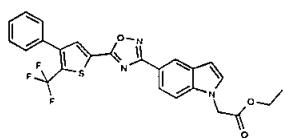
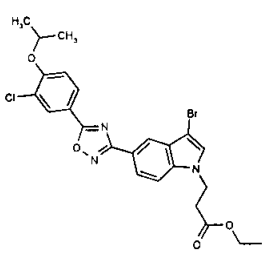


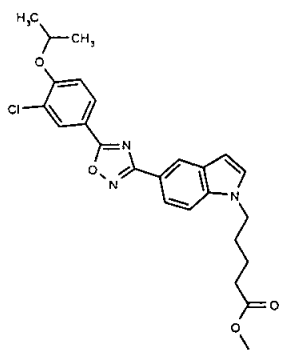
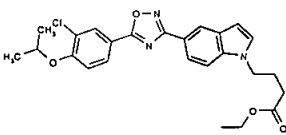
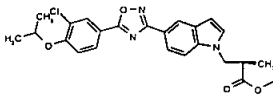
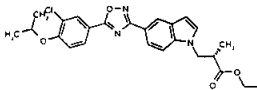
20 A 5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol (**D5**) (450mg, 1,27 mmol) disuelto en DMF (12ml) se añadió bromo (213mg, 1,35 mmol) gota a gota. Se agitó durante 15 minutos, se separó la DMF por evaporación, se añadió dietil éter (70ml) y se lavó con agua (2x70ml). Se secó sobre $MgSO_4$ y el disolvente se separó por evaporación. El residuo se cristalizó con dietil éter/hexano para dar el

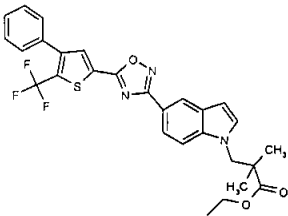
25 160 mg del compuesto del título en forma de un sólido blanco. δH (400 MHz, d_6 -DMSO) 1,37 (6H, d), 4,88 (1H, sept), 7,44 (1H, d), 7,59 (1H, dd), 7,72 (1H, d), 7,91

(1H, dd), 8,13-8,32 (3H, m). MS (ES) $C_{19}H_{15}^{79}BrClN_3O_2$ requiere 431; encontrado 432 (MH⁺).

- Los siguientes ésteres se prepararon de manera similar a la de los ejemplos
 5 previamente descritos (tal como **D6**) usando el indol y el agente alquilante
 apropiados. Los haluros de alquilo eran obtenibles en el mercado aparte de **D11** que
 se usó para preparar **D48**. Salvo indicación en contrario, las reacciones se realizaron
 en DMF. En algunas ocasiones las reacciones se trataron por un procedimiento
 acuoso mientras que en otras el material bruto se usó directamente en la etapa de
 10 hidrólisis tras la evaporación del disolvente de reacción.

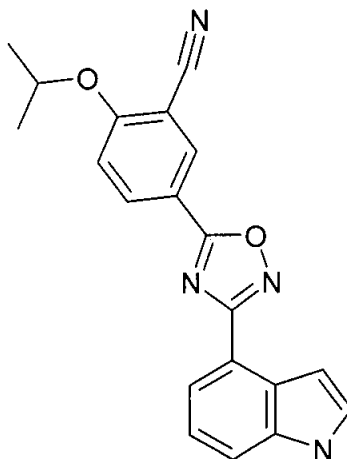
	Estructura	Nombre	Indol precursor	Comentarios	MH+
D42		(5-(5-(4-fenil-5-(trifluorometil)-2-tienil)-1,2,4-oxadiazol-3-il)-1H-indol-1-il)acetato de etilo	D2	disolvente DMPU en vez de DMF. Reacción a 100-120 °C en microondas.	—
D43		3-[3-bromo-5-(5-(3-cloro-4-[(1-metiletil)oxil]fenil)-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoato de etilo	D41	La reacción se calentó convencionalmente a 80 °C	534 para ⁸¹ Br ³⁵ Cl

D44		5-[5-(5-(3-cloro-4-[(1-metiletil)oxi]fenil)-1,2,4-oxadiazol-3-il)-1H-indol-1-il]pentanoato de metilo	D5	La reacción se calentó convencionalmente a 80 °C	468
D45		4-[5-(5-(3-cloro-4-[(1-metiletil)oxi]fenil)-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoato de etilo	D5	Reacción se calentó a 130°C en microondas. El material bruto se usó en la siguiente etapa después de la evaporación.	—
D46		(2R)-3-[5-(5-(3-cloro-4-[(1-metiletil)oxi]fenil)-1,2,4-oxadiazol-3-il)-1H-indol-1-il]-2-metilpropanoato de metilo	D5	Reacción se calentó a 140°C en microondas. El material bruto se usó en la siguiente etapa después de la evaporación.	—
D47		(2S)-3-[5-(5-(3-cloro-4-[(1-metiletil)oxi]fenil)-1,2,4-oxadiazol-3-il)-1H-indol-1-il]-2-metilpropanoato de etilo	D5	Reacción se calentó a 130°C en microondas. El material bruto se usó en la siguiente etapa después de la evaporación.	—

D48		2,2-dimetil-3-(5-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de etilo	D2	Reacción se calentó a 131-150 °C en microondas. El material bruto se usó en la siguiente etapa después de la evaporación.	540
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Descripción para D49

5 5-[3-(1H-indol-4-il)-1,2,4-oxadiazol-5-il]-2-[(1-metiletil)oxi]benzonitrilo (D49)



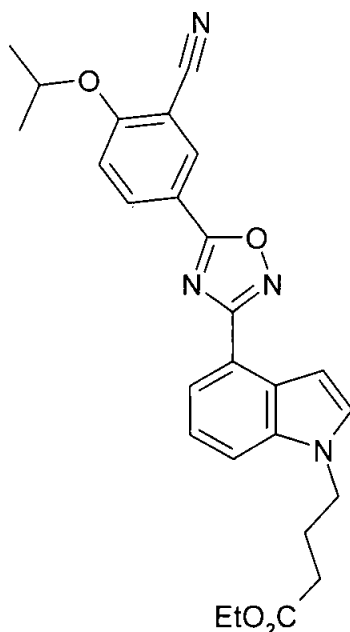
A ácido 3-ciano-4-[(1-metiletil)oxi]benzoico (se puede preparar como se describe en WO2005/58848) (500mg, 2,44 mmol) en DMF (15ml) se añadió EDAC (514mg, 2,67 mmol) y HOBt (367 mg, 2,67 mmol) y la disolución se dejó estar durante 30 minutos.

- 10 Se añadió *N*-hidroxi-1*H*-indol-4-carboximidamida (D9) (427 mg, 2,44 mmol) y se dejó estar durante 1 hora. A la disolución se añadieron EDAC (117mg, 0,61 mmol) y HOBt (84mg, 0,61 mmol) y se dejó estar durante 2 horas. A la disolución se añadieron EDAC (234,9mg, 1,22 mmol) y HOBt (167,7mg, 1,22 mmol) y se dejó estar durante una noche. Se calentó a 80 °C durante una noche, se enfrió y se
- 15 añadió EtOAc (30ml). Se lavó con agua (30ml), hidrógeno-carbonato de sodio sat. (30ml) y agua (30ml). Se secó sobre MgSO₄ y el disolvente se separó por evaporación. El residuo se trituró con dietil éter para dar 353 mg del compuesto del título en forma de un sólido de color marrón claro. δ H (400 MHz, d₆-DMSO) 1,39 (6H,

d), 4,94-5,03 (1H, m), 7,09-7,10 (1H, m), 7,30 (1H, t), 7,56-7,59 (2H, m), 7,67 (1H, d), 7,92 (1H, dd), 8,45 (1H, dd), 8,55 (1H, d), 11,52 (1H, s ancho). MS (ES) $C_{20}H_{16}N_4O_2$ requiere 344; encontrado 345 (MH^+).

5 **Descripción para D50**

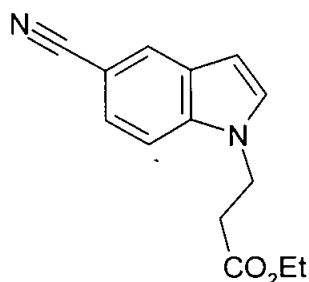
4-[4-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoato de etilo (D50)



Una mezcla de 5-[3-(1H-indol-4-il)-1,2,4-oxadiazol-5-il]-2-[(1-metiletil)oxi]benzonitrilo
10 **(D49)** (100mg, 0,29 mmol), 4-bromobutirato de etilo (85 mg, 0,44mmol) y carbonato
de cesio (189mg, 0,58 mmol) en DMF (2ml) se calentó a 80 °C durante 1 hora. Se
añadió 4-bromobutirato de etilo (85mg, 0,44 mmol) y se calentó durante una noche a
80 °C. Se añadieron 4-bromobutirato de etilo (85mg, 0,44 mmol) y carbonato de
cesio (189 mg, 0,58 mmol) y se calentó durante 24 horas. Se añadió 4-bromobutirato
15 de etilo (85mg, 0,44 mmol) y se calentó durante 24 horas. Se añadió 4-
bromobutirato de etilo (85mg, 0,44 mmol) y se calentó durante 6 horas. Se añadió
EtOAc (20ml) y se lavó con agua (20ml). Se secó sobre $MgSO_4$ y el disolvente se
separó por evaporación. El residuo se cristalizó en etanol para dar el compuesto del
título (55 mg) en forma de un sólido blanco. MS (ES) $C_{26}H_{26}N_4O_4$ requiere 458;
20 encontrado 459 (MH^+).

Descripción 51

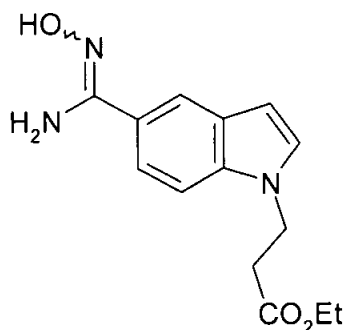
3-(5-ciano-1H-indol-1-il)propanoato de etilo (D51)



Una mezcla de 1*H*-indol-5-carbonitrilo (1,42g, 10 mmol), 3-bromopropanoato de etilo (1,92ml, 15 mmol) y carbonato de cesio (6,5g, 20 mmol) en DMF (50ml) se calentó a 80 °C durante 4 horas. Se enfrió la disolución, se añadió dietil éter (300ml) y se lavó con agua (3X 300ml). Se secó sobre MgSO₄ y el disolvente se separó por evaporación para dar 2,4g de aceite anaranjado pálido. Este producto bruto se usó en la siguiente etapa (preparación de **D52**).

Descripción para D52

10 3-{5-[(Hidroxiamino)(imino)metil]-1*H*-indol-1-il}propanoato de etilo

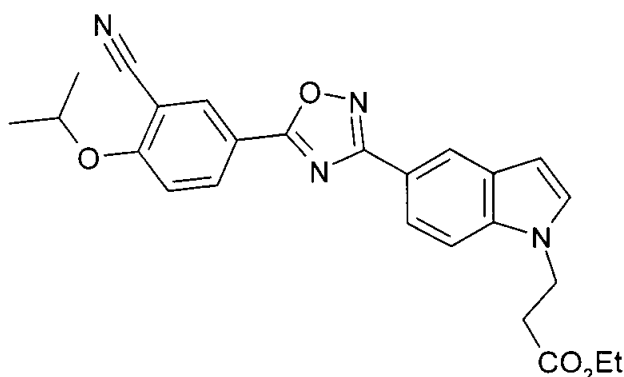


3-(5-ciano-1*H*-indol-1-il)propanoato de etilo (**D51**) (1,7g, 7,2 mmol), hidrocloreto de hidroxilamina (1,0g, 14,4 mmol) e hidrógeno-carbonato de sodio (2,42g, 28,9 mmol) se suspendieron en etanol (100ml) y se agitó a 50 °C durante 3 días. Se formó un solo producto pero quedó 15% de material de partida. Se enfrió, el material inorgánico se separó por filtración y el disolvente se separó por evaporación. El producto cristalizó en una mezcla de EtOAc, dietil éter y hexano para dar 1,9g del compuesto del título en forma de un sólido blanco. MS (ES) C₁₄H₁₇N₃O₃ requiere 275; encontrado 276. (MH⁺).

20

Descripción para D53

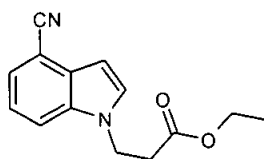
3-[5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1*H*-indol-1-il]propanoato de etilo (**D53**)



Ácido 3-ciano-4-[(1-metiletil)oxi]benzoico (se puede preparar como se describe en
5 WO2005/58848) (215mg, 1,05 mmol), EDAC (219mg, 1,14 mmol) y HOBt (156mg,
1,14 mmol) en DMF seca (10ml) se agitaron a TA durante 10 minutos. Se añadió 3-
{5-[(hidroxiamino)(imino)metil]-1*H*-indol-1-il}propanoato de etilo (**D52**) (288mg, 1,05
mmol) y se agitó durante 1 hora a RT. Se calentó a 80 °C durante 7 horas. La
disolución se enfrió y se añadió EtOAc (50ml). Se lavó con agua (50ml), hidrógeno-
10 carbonato de sodio sat. (50ml) y agua (50ml). Se secó sobre MgSO₄ y el disolvente
se separó por evaporación. El residuo se cristalizó en éter para dar 200 mg del
compuesto del título en forma de un sólido de color rosa muy pálido. MS (ES)
C₂₅H₂₄N₄O₄ requiere 444; encontrado 445 (MH⁺)

15 **Descripción para D54**

3-(4-ciano-1*H*-indol-1-il)propanoato de etilo (D54)

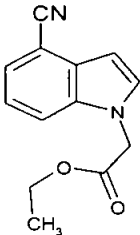


4-Cianoindol (2,5 g) se disolvió en DMF (7,5 ml). Se añadió Cs₂CO₃ (11,46 g)
seguido de 3-bromopropionato de etilo (3,38 ml). Esta mezcla se calentó a 80 °C
20 durante 40 minutos. Se añadió una porción adicional de DMF (5 ml) y se continuó
calentando a 80 °C durante 1 hora. La mezcla de reacción se evaporó y después se
disolvió en H₂O (200 ml) y extrajo con EtOAc (200 ml). Esto se evaporó para dar un
aceite amarillo (3,5 g) que se purificó en un cartucho 40+M Biotage, eluyendo con
una mezcla del 25 al 75% de Et₂O en hexano. Esto dio el compuesto del título (3,44
25 g) en forma de un aceite amarillo pálido. δ H (CDCl₃, 400MHz): 1,19 (3H, t), 2,82 (2H,

t), 4,12 (2H, q), 4,50 (2H, t), 6,71 (1H, d), 7,23-7,28 (1H, m), 7,33 (1H, d), 7,47 (1H, d), 7,60 (1H, dd). MS (ES): $C_{14}H_{14}N_2O_2$ requiere 242; encontrado 243 (MH^+).

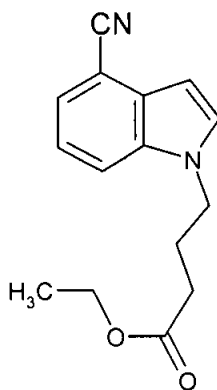
El siguiente ejemplo se preparó por un método similar a los descritos anteriormente.

- 5 La reacción no fue completa después del tratamiento, así que el material se volvió a someter a las condiciones de reacción con 0,2 equivalentes más de base y agente alquilante y el producto se purificó por trituración con éter.

de Ejemplo	Estructura	Nombre	MH^+
D55		(4-ciano-1H-indol-1-il)acetato de etilo	229

10 **Descripción para D56**

4-(4-Ciano-1H-indol-1-il)butanoato de etilo (D56)

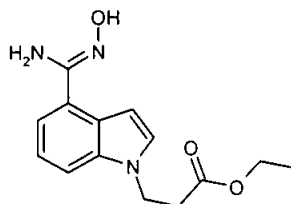


- 15 Se combinaron 4-cianoindol (5 g, 35,2 mmol), 4-bromobutanoato de etilo (10,29 g, 52,8 mmol) y carbonato de cesio (22,92 g, 70,3 mmol) y se calentó a 80 °C bajo argón durante 1 hora. La reacción se dejó enfriar y después se añadieron 150ml de dietil éter y la disolución orgánica se lavó con 3 x 150ml de H_2O . La fase orgánica se secó sobre $MgSO_4$, se filtró y se evaporó el disolvente. Se secó a alto vacío durante un fin de semana para dar el compuesto del título (8,25 g) en forma de un aceite anaranjado. δH (400 MHz, d_6 -DMSO). 1,13 (3H, t), 1,96-2,05 (2H, m), 2,26 (2H, t),

3,99 (2H, q), 4,29 (2H, t), 6,60 (1H, dd), 7,29 (1H, t aparente), 7,55 (1H, dd), 7,68 (1H, d), 7,90 (1H, d). MS (ES): $C_{15}H_{16}N_2O_2$ requiere 256; encontrado 257 (MH^+).

Descripción para D57

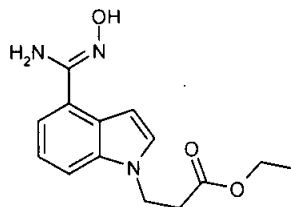
5 **3-{4-[(Hidroxiamino)(imino)metil]-1H-indol-1-il}propanoato de etilo (D57)**



3-(4-ciano-1H-indol-1-il)propanoato de etilo (**D54**) (3,44 g), $NH_2OH \cdot HCl$ (1,97 g) y Na_2CO_3 (5,96 g) se disolvieron en EtOH (75 ml). Esta mezcla se calentó a 50 °C durante una noche. Se añadió una porción adicional de $NH_2OH \cdot HCl$ (985 mg) y la
10 mezcla se agitó a 70 °C durante una noche. Después, la mezcla de reacción se filtró y evaporó para dar el compuesto del título (4,06 g). MS (ES): $C_{14}H_{17}N_3O_3$ requiere 275; encontrado 276 (MH^+)

Descripción para D57 (Procedimiento alternativo)

15 **3-{4-[(Hidroxiamino)(imino)metil]-1H-indol-1-il}propanoato de etilo (D57)**

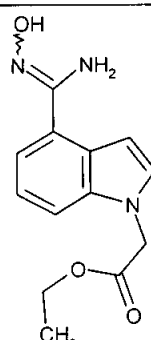


Una mezcla de 1H-indol-4-carbonitrilo (3,4 g, 23,92 mmol), 3-bromopropanoato de etilo (4,57 ml, 35,9 mmol) y carbonato de cesio (15,59 g, 47,8 mmol) se calentó a 80 °C durante 2 horas y se dejó estar durante una noche. Se añadió éter (400ml) y la
20 mezcla resultante se lavó con agua (3X400ml), se secó sobre $MgSO_4$ y evaporó para dar 6,6 g de aceite claro de color amarillo pálido.

El aceite N4111-30-A2 (6,6 g, 27,2 mmol), hidrocloreto de hidroxilamina (3,79 g, 54,5 mmol) y bicarbonato de sodio (9,15 g, 109 mmol) en etanol se agitaron a 50 °C durante una noche. Se añadió más hidrocloreto de hidroxilamina (2,3g) y se calentó
25 a 50 °C durante 24 horas. La reacción se filtró y el residuo se lavó con DCM (50ml). El disolvente se separó por evaporación y el residuo se trituroó con hexano para obtener el compuesto del título (4,2g) en forma de un sólido blanco. Se obtuvo más compuesto del título (1,0 g) en forma de un sólido blanco por trituroación de los

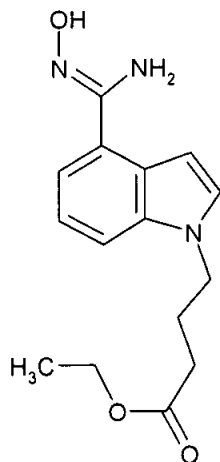
residuos. Los datos espectrales de masas fueron concordantes con la síntesis previa.

- El siguiente se preparó de manera similar a primer procedimiento **D57** descrito, se usó bicarbonato de sodio como base y la reacción se llevó a cabo a 55 °C.

de Ejemplo	Estructura	número del precursor	Nombre	MH ⁺
D58		D55	{4-[(hidroxiamino)(imino)metil]-1H-indol-1-il}acetato de etilo	262

Descripción para D59

4-{4-[(hidroxiamino)(imino)metil]-1H-indol-1-il}butanoato de etilo (D59)



10

4-(4-ciano-1H-indol-1-il)butanoato de etilo (**D56**) (8,25 g, 32,2 mmol) se disolvió en EtOH y se trató con NH₂OH.HCl (4,47 g, 64,4 mmol) y NaHCO₃ (8,11 g, 97 mmol) y se calentó a 55°C durante 1 día y dos noches. Se añadieron cantidades adicionales de NH₂OH.HCl (500 mg) y NaHCO₃ (500 mg) y la reacción se calentó durante otras 3 horas y después se separó la materia inorgánica por filtración, lavando bien con EtOH. El disolvente se evaporó y el residuo se secó a alto vacío. La tritución con

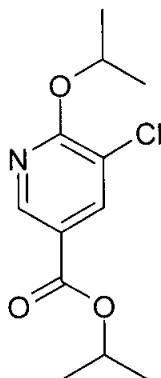
15

éter y dcm proporcionó dos lotes del compuesto del título N2668-20-A8 (5,14 g) y N2668-20-A9 (976 mg). δ H (400 MHz, d_6 -DMSO) 1,15 (3H, t), 1,98 (2H, quintete aparente), 2,25 (2H, t), 4,03 (2H, q), 4,21 (2H, t), 5,73 (2H, s ancho), 6,82 (1H, dd), 7,15 (1H, t aparente), 7,27 (1H, dd), 7,35 (1H, d), 7,51 (1H, d), 9,58 (1H, s ancho).

5 MS (ES): $C_{15}H_{19}N_3O_3$ requiere 289; encontrado 290 (MH^+).

Descripción para D60

5-Cloro-6-[(1-metiletil)oxi]-3-piridinacarboxilato de 1-metiletilo (D60)

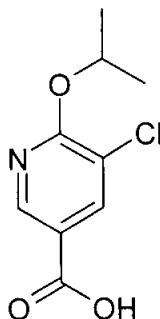


10 El ácido 5-cloro-6-hidroxi-3-piridinacarboxílico (1g, 5,76 mmol) se suspendió en tolueno (200ml) y se trató con carbonato de plata (3,97 g, 14,40 mmol) y 2-yodopropano (3,46 ml, 34,6 mmol) y se agitó a TA en la oscuridad durante 3 días. LC/MS indicó 2/3 de producto. Se añadió 2-yodopropano (3ml) y se agitó durante 24 horas. LC/MS indicó 80% de producto. Se añadió EtOAc (200ml) y se lavó con agua

15 (200ml) + $NaHCO_3$ sat. (50ml) seguido de agua (200ml). Se secó sobre $MgSO_4$ y el disolvente se separó por evaporación para dar 1,0g del compuesto del título en forma de un aceite incoloro claro. MS (ES^+) $C_{12}H_{16}^{35}ClNO_3$ requiere 257; encontrado 257.

20 Descripción para D61

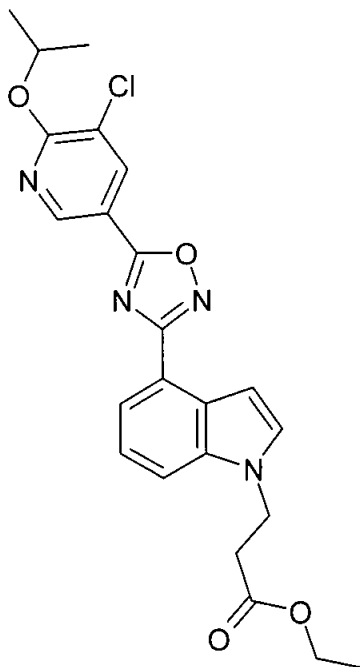
5-Cloro-6-[(1-metiletil)oxi]-3-piridinacarboxílico (D61)



- 5-Cloro-6-[(1-metiletil)oxi]-3-piridinacarboxilato de 1-metiletilo (**D60**) (1,6 g, 6,21 mmol) en isopropanol (70 ml) y agua (35,0 ml) se trataron con hidróxido de sodio 2N (6,21 ml, 12,42 mmol) y se agitaron durante 3 horas para dar un solo producto. Se separó el IPA por evaporación, se aciduló con ácido acético glacial y el producto se extrajo en EtOAc (100ml). Se secó sobre MgSO_4 y el disolvente se separó por evaporación para dar 1,30 g del compuesto del título en forma de un sólido blanco. MS (ES) $\text{C}_9\text{H}_{10}^{35}\text{ClNO}_3$ requiere 215; encontrado 214 ($\text{M}-\text{H}^+$).

10 **Descripción para D62**

3-[4-(5-{5-Cloro-6-[(1-metiletil)oxi]-3-piridinil)-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoato de etilo (D62)



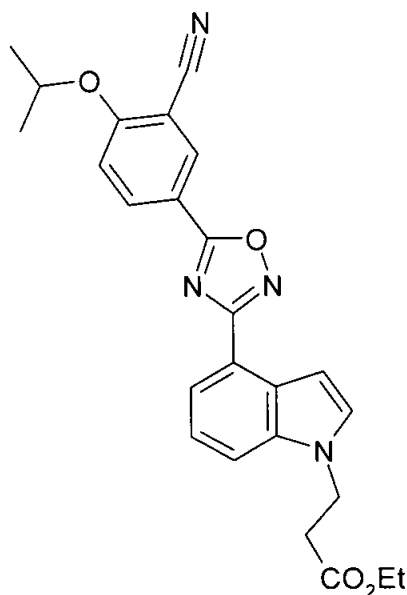
- A 5-cloro-6-[(1-metiletil)oxi]-3-piridinacarboxílico (**D61**) (1,504 g, 6,97 mmol) en DMF
seca (30ml) se añadió EDC (1,604 g, 8,37 mmol) y HOBT (1,282 g, 8,37 mmol). Se
agitó la disolución a TA durante 10 minutos y después se añadió 3-[4-
[(hidroxiamino)(imino)metil]-1H-indol-1-il]propanoato de etilo (N4111-31-A4) (**D57**)
(1,92 g, 6,97 mmol). La mezcla se agitó durante 30 minutos. LC/MS indicó un
producto (Intermedio). La disolución se calentó a 80 °C durante 2 horas. Se dejó
estar durante una noche a TA y después se calentó 80 °C durante 2 horas más para
dar reacción completa. Se enfrió y se añadió EtOAc (250ml). El EtOAc se lavó con
 NaHCO_3 sat. (150ml) seguido de agua (2X 200ml). Se secó sobre MgSO_4 y el

disolvente se separó por evaporación. El residuo se sometió a cromatografía sobre Biotage (EtOAc/hexano 1:2). Al evaporar la mayor parte del disolvente de las fracciones limpias y añadir hexano se formó un precipitado blanco. El sólido se separó por filtración para obtener 1,1 mg del producto del título. MS (ES) $C_{23}H_{23}^{35}CIN_4O_4$ requiere 454; encontrado 455 (MH^+).

Descripción para D63

3-[4-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoato de etilo (D63)

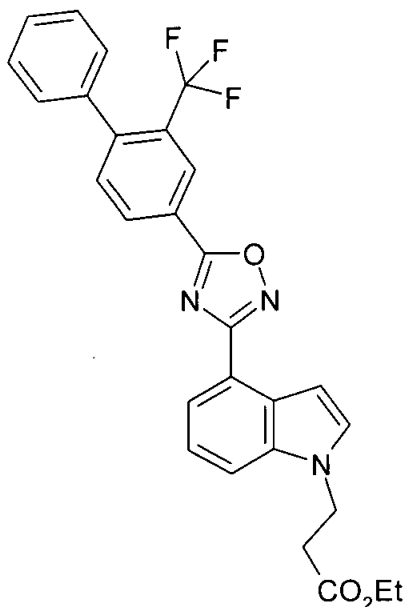
10



El ácido 3-ciano-4-[(1-metiletil)oxi]benzoico (se puede preparar como se describe en WO2005/58848) (113mg, 0,55mmol), EDAC (115mg, 0,60 mmol) y HOBt (82mg, 0,60 mmol) se disolvieron en DMF (5ml) y se dejó estar durante 15 minutos. Se añadió 3-[4-[(hidroxiamino)(imino)metil]-1H-indol-1-il]propanoato de etilo (D52) (150mg, 0,55 mmol) y se dejó estar durante una noche a RT. Se calentó la disolución a 80 °C durante 2 horas. LC/MS indicó producto mayoritariamente. Después de calentar durante unas pocas horas más no hubo ningún cambio. Se añadió EtOAc (20ml) y se lavó con agua (30ml). Se lavó con hidrógeno-carbonato de sodio saturado (30ml) y agua (2x30ml). Se secó sobre $MgSO_4$ y el disolvente se separó por evaporación para dar 81 g del compuesto del título en forma de un sólido marrón pálido. MS (ES) $C_{25}H_{44}N_4O_4$ requiere 444; encontrado 445 (MH^+).

Descripción para D64

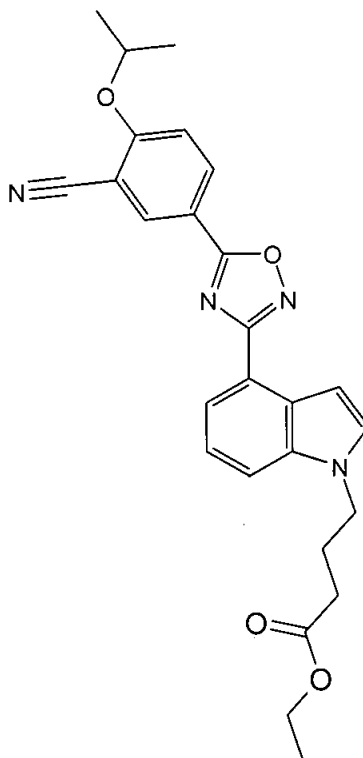
3-(4-{5-[2-(Trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-1*H*-indol-1-il)propanoato de etilo (D64)



- 5 A 2-(trifluorometil)-4-bifenilcarboxílico (**D29**) (146mg, 0,55mmol) en DMF (5ml) se
añadió EDC (115mg, 0,60 mmol) y HOBt (82mg, 0,60 mmol) y la disolución se dejó
estar durante 15 minutos. Se añadió 3-{4-[(hidroxiamino)(imino)metil]-1*H*-indol-1-
il}propanoato de etilo (**D57**) (150mg, 0,55 mmol) y se agitó a TA durante 1 hora. La
mezcla se calentó a 80°C durante 1 hora y después se calentó durante una noche.
Se enfrió y después se añadió EtOAc (20ml). Se lavó con agua (20ml), hidrógeno-
10 carbonato de sodio acuoso sat. (20ml) y agua (20ml). Se secó sobre MgSO₄ y
después se evaporó el disolvente. El residuo se trituró con etanol para dar 157 mg
del compuesto del título en forma de un sólido blanco. δ H (400 MHz, d₆-DMSO) 1,11
(3H, t), 2,90 (2H, t), 4,02 (2H, q), 4,55 (2H, t), 7,10 (1H, d), 7,32-7,48 (3H, m), 7,49-
7,61 (3H, m), 7,61 (1H, d), 7,73-7,84 (2H, m), 8,00 (1H, d), 8,53-8,56 (2H, m). MS
15 (ES) C₂₈H₂₂F₃N₃O₃ requiere 505; encontrado 506 (MH⁺).

Descripción para D65 (alternativa a la Descripción para D50)

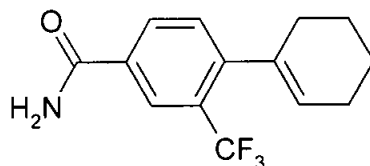
4-[4-{5-[3-Ciano-4-[(1-metiletil)oxi]fenil]-1,2,4-oxadiazol-3-il}-1*H*-indol-1-il]butanoato de etilo (D65)



- Una mezcla de ácido 3-ciano-4-[(1-metiletil)oxi]benzoic acid (se puede preparar como se describe en WO2005/58848) (1,21g, 5,88 mmol), EDC (1,35g, 7,05 mmol) y HOBt (1,08g, 7,05 mmol) en DMF seca (85 ml) se agitó durante 20 minutos a RT.
- 5 Se añadió 4-{4-[(hidroxiamino)(imino)metil]-1H-indol-1-il}butanoato de etilo (D59) (1,70g, 5,88 mmol) y se agitó a TA durante 1 hora. La mezcla se calentó a 80 °C durante 5 horas y se dejó estar durante una noche a RT. Se calentó a 80 °C durante 6 horas, después se separó por evaporación la DMF. Se añadió EtOAc (200ml) y se lavó con NaHCO₃ sat. (200ml) y agua (200ml). Se secó sobre MgSO₄ y el disolvente
- 10 se separó por evaporación. El residuo se sometió a cromatografía usando el Biotage (EtOAc/hexano 1:2) y se evaporaron las fracciones más limpias para dar 1,42g el compuesto del título en forma de un sólido blanco. δ H (400 MHz, d₆-DMSO) 1,15 (3H, t), 1,39 (6H, d), 2,04 (2H, quintete aparente), 2,24 (2H, t), 4,00 (2H, q), 4,31 (2H, t), 4,94-5,04 (1H, m), 7,10 (1H, dd), 7,31 (1H, t), 7,56-7,60 (2H, m), 7,77 (1H, d),
- 15 7,95 (1H, d), 8,45 (1H, dd), 8,56 (1H, d). MS (ES) C₂₆H₂₆N₄O₄ requiere 458; encontrado 459 (MH⁺).

Descripción para D66

4-(1-Ciclohexen-1-il)-3-(trifluorometil)benzamida (D66)

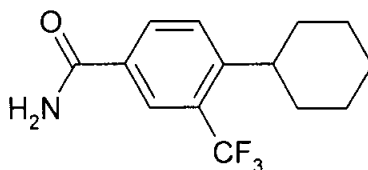


4-Bromo-3-(trifluorometil)benzonitrilo (comercial) (1,2 g, 4,80 mmol), ácido 1-ciclohexen-1-ilborónico (0,907 g, 7,20 mmol), metóxido de sodio (0,778 g, 14,40 mmol) y cloruro de bis(trifenilfosfina)paladio(II) (0,337 g, 0,480 mmol) se añadieron a metanol seco (12 mL) y la mezcla se calentó en el microondas a 80 °C durante 10 minutos. La mezcla de reacción se repartió entre acetato de etilo (40 mL) y agua (40 mL) y después la fase orgánica se lavó con más agua (40 mL). La fase orgánica se secó (MgSO₄), filtró y se separó el disolvente a vacío. El producto bruto se purificó por cromatografía instantánea sobre sílice, eluyendo con 0-75 % de acetato de etilo en hexano para dar el compuesto del título en forma de un sólido blanco (1,02 g). δ H (CDCl₃, 400 MHz): 8,09 (1H, m), 7,90 (1H, dd), 7,32 (1H, d), 6,3-5,8 (2H, m) 5,61 (1H, s), 2,25-2,13 (4H, m), 1,80-1,60 (4H, m). MS (ES): C₁₄H₁₄F₃NO requiere 269; encontrado 270 (MH⁺).

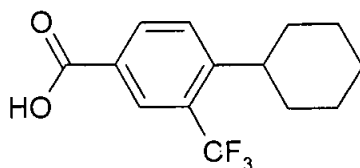
Descripción para D67

GSK1929583A, N2123-11-A2

4-Ciclohexil-3-(trifluorometil)benzamida (D67)



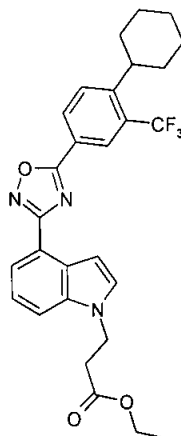
4-(1-Ciclohexen-1-il)-3-(trifluorometil)benzamida (**D66**) (850 mg, 3,16 mmol) se disolvió en metanol (63 ml) y se hidrogenó usando un H-Cube, usando paladio sobre carbono a 40 °C con un caudal de 2 mL/min. El disolvente se separó a vacío para dar el compuesto del título en forma de un sólido blanco (822 mg). δ H (CDCl₃, 400 MHz): 8,08 (1H, d), 7,94 (1H, dd), 7,52 (1H, d), 6,54 (2H, brs), 2,97 (1H, m), 1,90-1,75 (5H, m), 1,50-1,22 (5H, m). MS (ES): C₁₄H₁₆F₃NO requiere 271; encontrado 272 (MH⁺).

Descripción para D68**Ácido 4-ciclohexil-3-(trifluorometil)benzoico (D68)**

5

A una disolución de 4-ciclohexil-3-(trifluorometil)benzamida (**D67**) (822 mg, 3,03 mmol) en etanol (40 ml) se añadió hidróxido de potasio (1,700 g, 30,3 mmol) y agua (5 ml) y la reacción se calentó a 90 °C, temperatura de bloqueo, durante 3 h y se agitó a temperatura ambiente durante 16 h. Se añadió más hidróxido de potasio (1,700 g, 30,3 mmol) y la reacción se calentó a reflujo durante 27 h. Se añadieron 5 mL más de agua y la reacción se calentó durante 66 horas (fin de semana). La mezcla de reacción se concentró a vacío y el residuo se repartió entre acetato de etilo (25 mL) y ácido clorhídrico acuoso (2M, 25 mL). La capa acuosa se extrajo además con acetato de etilo (25 mL) y las fases orgánicas combinadas se secaron (MgSO₄), filtraron y se separó el disolvente a vacío para dar el compuesto del título en forma de un sólido blanco (737 mg). δ H (metanol-d₄, 400 MHz): 8,24 (1H, d), 8,18 (1H, dd), 7,68 (1H, d), 2,98 (1H, t), 1,72-1,95 (5H, m), 1,30-1,58 (5H, m). MS (ES): C₁₄H₁₅F₃O₂ requiere 272; encontrado 271 (M-H⁺).

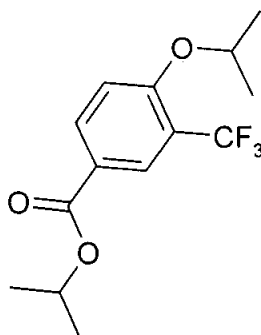
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Descripción para D69**3-(4-{5-[4-Ciclohexil-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de etilo (D69)**

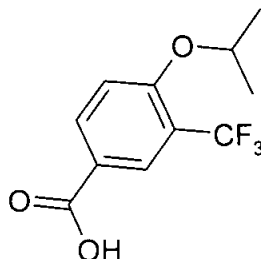
Una solución de ácido 4-ciclohexil-3-(trifluorometil)benzoico (**D68**) (148 mg, 0,545 mmol), EDC (115 mg, 0,599 mmol) y HOBt (92 mg, 0,599 mmol) en DMF (5 ml) se agitó durante 10 min antes de la adición de 3-{4-[(hidroxiamino)(imino)metil]-1H-indol-1-il}propanoato de etilo (**D57**) (150 mg, 0,545 mmol). La reacción se agitó durante 30 min a temperatura ambiente seguido de 16 h a 80 °C. La mezcla de reacción se repartió entre acetato de etilo (25 mL) y agua (25 mL) y la fase orgánica se lavó con bicarbonato de sodio acuoso (25 mL) y después agua (25 mL). La fase orgánica se secó (separador de fases) y se separó el disolvente *a vacío*. El producto bruto se purificó por MDAP. Algo de la mezcla sometida a MDAP había precipitado y se trituró con etanol y filtró. Los sólidos blancos se combinaron para dar el compuesto del título (63 mg). MS (ES): $C_{28}H_{28}F_3N_3O_3$ requiere 511; encontrado 512 (MH^+).

Descripción para D70

15 **4-[(1-Metiletil)oxi]-3-(trifluorometil)benzoato de 1-metiletilo (D70)**



Una mezcla de ácido 4-hidroxi-3-(trifluorometil)benzoico (comercial) (450 mg, 2,18 mmol), 2-yodopropano (435 μ L, 4,36 mmol) y carbonato de potasio (603 mg, 4,36 mmol) en N,N'-dimetilformamida (40 mL) se calentó a 70 °C durante 4 h antes de añadir más 2-yodopropano (218 μ L, 2,18 mmol) y se continuó calentando durante 18 h. El sólido inorgánico se separó por filtración y se lavó con acetato de etilo. El filtrado se concentró *a vacío* y se repartió entre acetato de etilo (150 mL) y agua (150 mL) que contenía algo de hidróxido de sodio acuoso. La capa orgánica se secó (separador de fases) y concentró *a vacío* para dar el compuesto del título bruto en forma de un aceite amarillo (704 mg). MS (ES): $C_{14}H_{17}F_3O_3$ requiere 290; encontrado 291 (MH^+).

Descripción para D71**Ácido 4-[(1-metiletil)oxi]-3-(trifluorometil)benzoico (D71)**

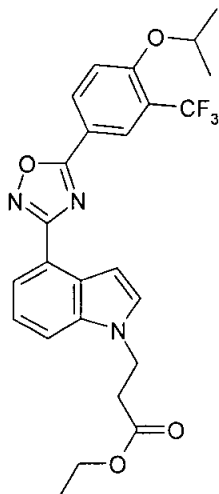
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A una mezcla de 4-[(1-metiletil)oxi]-3-(trifluorometil)benzoato de 1-metiletilo (**D70**) (704 mg, 2,43 mmol) en etanol (110 mL) se añadió hidróxido de sodio acuoso (2M, 12,2 mL, 24,3 mmol) y la reacción se calentó a reflujo durante 1 h. La mezcla se concentró *a vacío* y el residuo se repartió entre acetato de etilo (100 mL) y agua (100 mL) y se aciduló con ácido clorhídrico acuoso (2M, 13 mL). La capa acuosa se extrajo además con acetato de etilo (100 mL) y las capas orgánicas combinadas se secaron y concentraron *a vacío* para dar el compuesto del título en forma de un sólido amarillo (563 mg). δ H (metanol- d_4 , 400 MHz): 8,21-8,17 (2H, m), 7,26 (1H, d), 4,84 (1H, septete), 1,38 (6H, d). MS (ES): $C_{11}H_{11}F_3O_3$ requiere 248; encontrado 247 ($M-H^+$).

15

Descripción para D72**3-(4-{5-[4-[(1-Metiletil)oxi]-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-****il)propanoato de etilo (D72)**

20



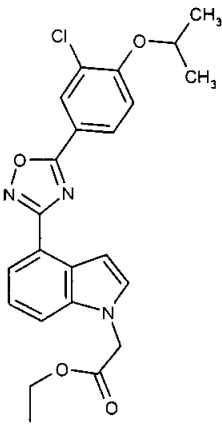
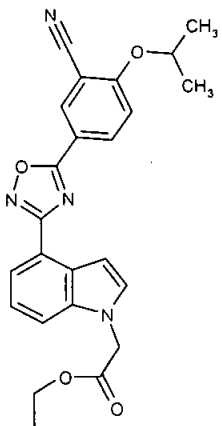
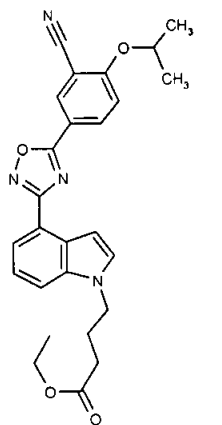
Ácido 4-[(1-metiletil)oxi]-3-(trifluorometil)benzoico (**D71**) (136 mg, 0,55 mmol), EDC (116 mg, 0,61 mmol) y HOBt (82 mg, 0,61 mmol) se agitaron en N,N-dimetilformamida (5 mL) durante 20 min. Se añadió 3-{4-[(hidroxiamino)(imino)metil]-1H-indol-1-il}propanoato de etilo (**D57**) (150 mg, 0,55 mmol) y la reacción se agitó a temperatura ambiente durante 3 h y después a 80 °C durante 18 h. La mezcla de reacción se repartió entre acetato de etilo (25 mL) y agua (25 mL). La capa orgánica se lavó con bicarbonato de sodio acuoso (25 mL) y agua (25 mL) antes de secarla (separador de fases), se filtró y concentró a vacío. El residuo se trituró con etanol para dar el compuesto del título (85 mg). δ H (d_6 -DMSO, 400 MHz): 8,44 (1H, dd), 8,35 (1H, d), 7,95 (1H, d), 7,81 (1H, d), 7,62-7,58 (2H, m), 7,36 (1H, t aparente), 7,07 (1H, d), 4,99 (1H, septete), 4,54 (2H, t), 4,02 (2H, q), 2,89 (2H, t), 1,36 (6H, d), 1,11 (3H, t). EM (ES⁺): C₂₅H₂₄F₃N₃O₄ requiere 487; encontrado 488 (MH⁺).

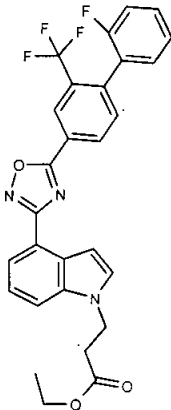
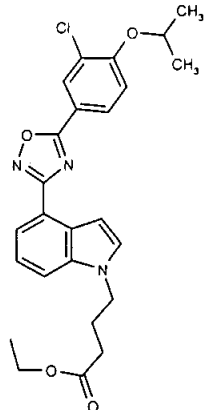
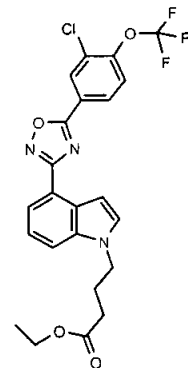
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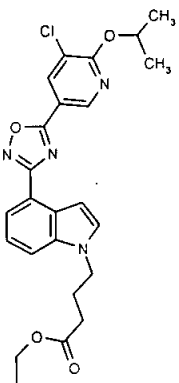
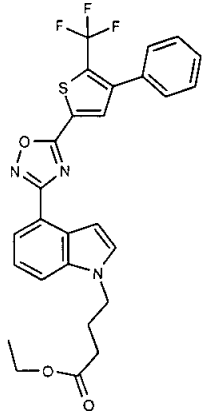
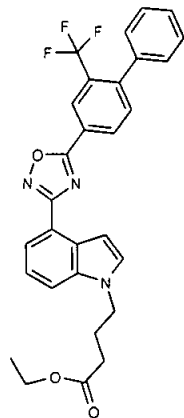
Los siguientes ejemplos se prepararon por un método similar a los descritos anteriormente. En ocasiones fue necesario añadir más EDAC (hasta 2,6 equiv) y en el caso de **D80** fue necesario elevar la temperatura a 120 °C. El tratamiento era acuoso o alternativamente el disolvente se separó a vacío. En el caso de **D92** se añadió etanol a la mezcla de reacción y el precipitado resultante se filtró. Los compuestos se purificaron o bien por trituración, MDAP, normal or cromatografía en fase reversa.

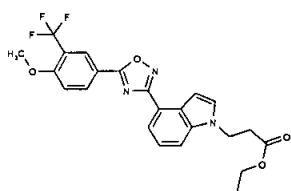
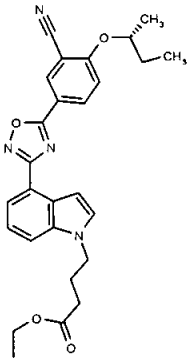
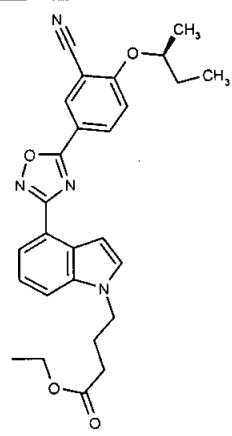
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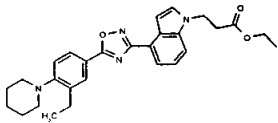
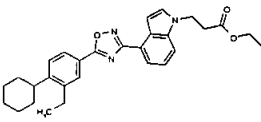
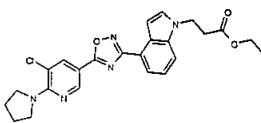
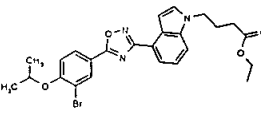
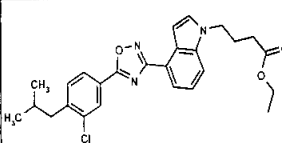
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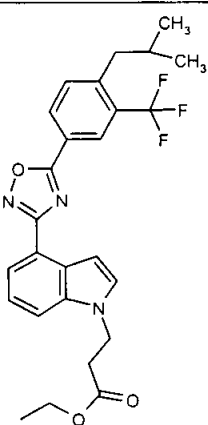
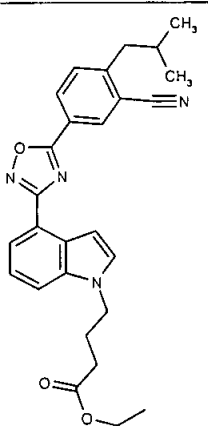
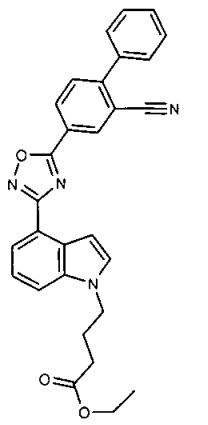
	Estructura	Precursores	Nombre	MH ⁺
D73		D58 & D4	[4-(5-(3-cloro-4-[(1-metiletil)oxi]fenil)-1,2,4-oxadiazol-3-il)-1H-indol-1-il]acetato de etilo	440/ 442
D74		D58	[4-(5-(3-ciano-4-[(1-metiletil)oxi]fenil)-1,2,4-oxadiazol-3-il)-1H-indol-1-il]acetato de etilo	431
D75		D59	4-[4-(5-(3-ciano-4-[(1-metiletil)oxi]fenil)-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoato de etilo	459

D76		D57 & D30	3-(4-(5-(2'-fluoro-2-(trifluorometil)-4-bifenilil)-1,2,4-oxadiazol-3-il)-1H-indol-1-il)propanoato de etilo	524
D77		D59 & D4	4-[4-(5-(3-cloro-4-[(1-metiletil)oxi]fenil)-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoato de etilo	468
D78		D59	4-[4-(5-(3-cloro-4-[(trifluorometil)oxi]fenil)-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoato de etilo	494

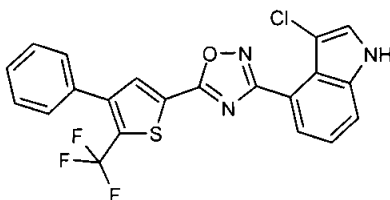
D79		D59 & D61	4-[4-(5-[5-cloro-6-[(1-metiletil)oxi]-3-piridinil]-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoato de etilo	469
D80		D59	4-(4-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)butanoato de etilo	526
D81		D59 & D29	4-(4-{5-[2-(trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)butanoato de etilo	520

D82		D57	3-(4-{5-[4-(metiloxi)-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de etilo	460
D83		D59 & D38	4-{4-[5-(3-ciano-4-[(1R)-1-metilpropil]oxi)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il}butanoato de etilo	473
D84		D59 & D36	4-{4-[5-(3-ciano-4-[(1S)-1-metilpropil]oxi)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il}butanoato de etilo	473

D85		D57 & D13	3-(4-{5-[3-etil-4-(1-piperidinil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de etilo	473
D86		D57 & D19	3-{4-[5-(4-ciclohexil-3-etilfenil)-1,2,4-oxadiazol-3-il]-1H-indol-1-il}propanoato de etilo	472
D87		D57 & D15	3-(4-{5-[5-cloro-6-(1-pirrolidinil)-3-piridinil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de etilo	466
D88		D59 & D21	4-[4-(5-{3-bromo-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoato de etilo	512
D89		D59 & D24	4-(4-{5-[3-cloro-4-(2-metilpropil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)butanoato de etilo	466

D90		D57 & D34	3-(4-{5-[4-(2-metilpropil)-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de etilo	486
D91		D59 & D32	4-(4-{5-[3-ciano-4-(2-metilpropil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)butanoato de etilo	457
D92		D59 & D27	4-{4-[5-(2-ciano-4-bifenilil)-1,2,4-oxadiazol-3-il]-1H-indol-1-il}butanoato de etilo	477

Descripción para D93**3-Cloro-4-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol****(D93)**



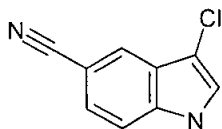
Este material se preparó de una manera similar a **D7** (CQ107723-108A2) a partir de **D10** excepto que la reacción se agitó durante cuatro horas en vez de durante una noche. MS (ES): $C_{21}H_{11}ClF_3N_3OS$ requiere 445; encontrado 446 (MH^+).

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Descripción para D94

3-Cloro-1H-indol-5-carbonitrilo (D94)

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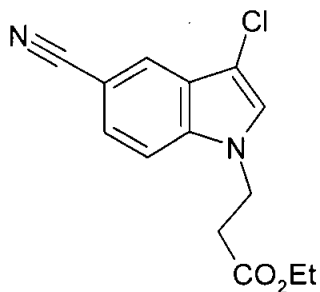


A una disolución de 5-cianoindol (3,0g, 21mmol) en DMF seca (50ml) se añadió *N*-clorosuccinimida (2,94g, 22 mmol) y la disolución se agitó a temperatura ambiente durante 1 hora. La disolución se dejó estar a lo largo del fin de semana. LC/MS indicó un solo producto. Se añadió acetato de etilo (150ml) y dietil éter (50ml) y se lavó con agua (3X 300ml). Se secó sobre $MgSO_4$ y el disolvente se separó por evaporación para dar 3,9 g del compuesto del título en forma de un sólido amarillo pálido. δH (400 MHz, d_6 -DMSO) 7,54 (1H, dd), 7,61 (1H, dd), 7,78 (1H, d), 8,01-8,02 (1H, m), 12,2 (1H, s ancho). MS (a partir de LCMS de la mezcla de reacción) (ES): $C_9H_5ClN_2$ requiere 176; encontrado 177 (MH^+).

20

Descripción para D95

3-(3-Cloro-5-ciano-1H-indol-1-il)propanoato de etilo (D95)

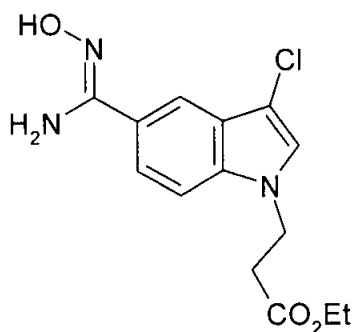


Una mezcla de 3-cloro-1*H*-indol-5-carbonitrilo (**D94**) (1,8g, 10mmol), 3-bromopropionato de etilo (1,92ml, 15mmol), carbonato de cesio (6,5g, 20mmol) y DMF (50ml) se calentó a 80 °C durante 4 horas para dar reacción completa.

- 5 Después de dejar enfriar la mezcla a temperatura ambiente se añadió dietil éter (300ml) y la disolución se lavó con agua (3X300ml). Se secó sobre MgSO₄ y el disolvente se separó por evaporación para dar un sólido marrón. El sólido se trituro con una mezcla de dietil éter y hexano para obtener 2,5g del compuesto del título como un sólido de color canela. El producto bruto se usó en la siguiente etapa
- 10 (síntesis de **D96**).

Descripción para D96

- 15 3-{3-cloro-5-(hidroxiamino)(imino)metil}-1*H*-indol-1-il}propanoato de etilo (**D96**)



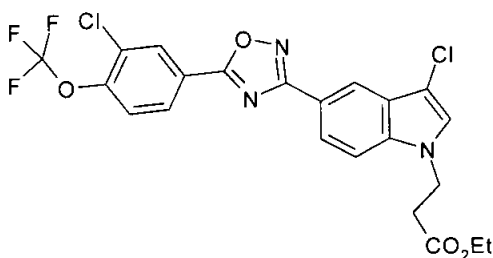
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Una mezcla de 3-(3-cloro-5-ciano-1*H*-indol-1-il)propanoato de etilo (**D95**) (2,0g, 7,2 mmol), hidrocloreuro de hidroxilamina (1,0g, 14,4 mmol), hidrógeno-carbonato de sodio (2,42g, 28,9 mmol) y etanol (100ml) se calentó a 50 °C a lo largo del fin de

semana. Todavía quedaba 25% de material de partida presente, según LC/MS. Se añadió hidrocloreto de hidroxilamina (0,5g, 7,2 mmol) e hidrógeno-carbonato de sodio (1,2g, 14,3 mmol) y se calentó a 50 °C durante 24 horas. Sólo quedó una pequeña cantidad de material de partida presente, así que se decidió tratar la
5 reacción. El material inorgánico se retiró por filtración. El disolvente se evaporó y el residuo se trituró usando acetato de etilo y dietil éter para dar 1,9 g del compuesto del título en forma de un sólido amarillo pálido. MS (ES) $C_{14}H_{16}ClN_3O_3$ requiere 309; encontrado 310 (MH^+).

10 **Descripción para D97**

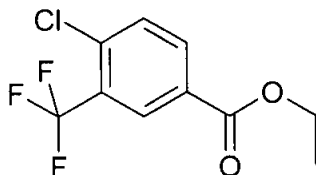
3-[3-Cloro-5-(5-{3-cloro-4-[(trifluorometil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoato de etilo (D97)



15

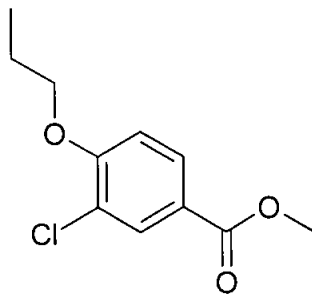
Ácido 3-cloro-4-[(trifluorometil)oxi]benzoico (comercial: ABCR) (168mg, 0,70 mmol) agitando en DMF (6ml) se trató con EDC (146mg, 0,76 mmol) seguido de HOBt (104mg, 0,76 mmol). La disolución resultante se agitó durante 15 minutos. Se
20 añadió 3-{3-cloro-5-[(hidroxiamino)(imino)metil]-1H-indol-1-il}propanoato de etilo (D96) (216mg, 0,70 mmol) y se agitó a TA durante 45 minutos. La disolución se calentó a 80 °C durante 6 horas y después se dejó estar a temperatura ambiente durante una noche. LC/MS indicó un solo producto. Se añadió EtOAc (50ml) y se lavó con agua (50ml), hidrógeno-carbonato de sodio acuoso saturado (50ml) y agua
25 (50ml). Se secó sobre $MgSO_4$ y el disolvente se separó por evaporación. El residuo se cristalizó en etanol para dar 200mg de sólido blanco. δH (400 MHz, d_6 -DMSO) 1,11 (3H, t), 2,92 (2H, t), 4,00 (2H, q), 4,49 (2H, t), 7,75 (1H, s), 7,80 (1H, d), 7,85 (1H, dd), 7,95 (1H, dd) 8,23 (1H, d) 8,30 (1H, dd), 8,47 (1H, d). MS (ES) $C_{22}H_{16}^{35}Cl^{37}ClF_3N_3O_4$ requiere 515; encontrado 516 (MH^+).

30

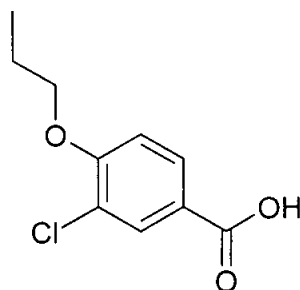
Descripción para D98 (alternativa a la Descripción para D28)**4-Cloro-3-(trifluorometil)benzoato de etilo (D98)**

Una solución de ácido 4-cloro-3-trifluorometil benzoico (10 g, 44,5 mmol) en etanol
5 (10 ml) se repartió en partes iguales entre dos viales de microondas. Se añadió
ácido sulfúrico concentrado (0,75 ml) a cada vial (1,5 ml en total). Las reacciones se
caientaron en el microondas a 120°C durante 30 minutos en total. Las mezclas de
reacción se combinaron y se concentraron al vacío. El residuo se repartió entre
EtOAc (100 ml) y bicarbonato de sodio aq. (100 ml), la fase orgánica se separó, se
10 lavó con bicarbonato de sodio aq. (100 ml) y agua (2 x 100 ml) y después se secó
(separador de fases) y se separó el disolvente *a vacío* para dar el compuesto del
título (4,126 g) en forma de un aceite incoloro. δ H (400 MHz, metanol- d_4) 1,40 (3H,
t), 4,41 (2H, cuartete), 7,76 (1H, d), 8,22 (1H, dd), 8,34 (1H, d).

15

Descripción para D99**3-Cloro-4-(propiloxi)benzoato de metilo (D99)**

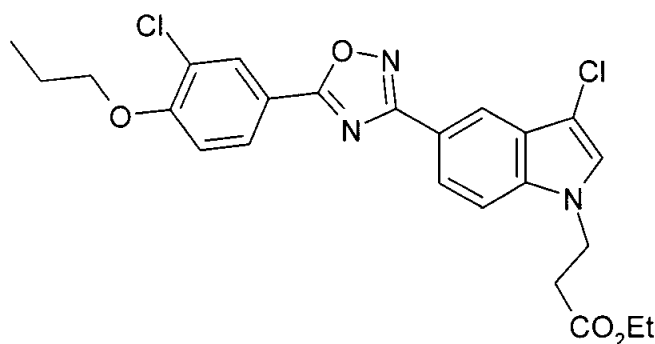
4-Hidroxi-3-clorobenzoato de metilo (10 g, 53,6 mmol) se disolvió en DMF (110 ml) y
20 después se añadió carbonato de potasio (14,8 g, 107,2 mmol) seguido de yoduro de
n-propilo (10,4 ml, 107,2 mmol). La reacción se se calentó a 70 °C durante una
noche, filtró y después el filtrado se repartió entre EtOAc y agua. La capa orgánica se
separó, se secó y evaporó para dar el compuesto del título en forma de un aceite
amarillo (12,37 g). δ H (400 MHz, d_6 -DMSO) 1,00 (3H, t), 1,72-1,92 (2H, m), 3,82 (3H,
s), 4,10 (2H, t), 7,24 (1H, d), 7,85-8,10 (2H, m). MS (ES) $C_{11}H_{13}^{35}ClO_3$ requiere 228;
25 encontrado 229 (MH^+).

Descripción para D100**Ácido 3-cloro-4-(propiloxi)benzoico (D100)**

- Una solución de 3-cloro-4-(propiloxi)benzoato de metilo (**D99**) (12,22 g, 0,053 mol) en etanol (40 ml) y NaOH 2M aq. (40 ml) se calentó a 60 °C durante 3 horas. La reacción se dejó enfriar y después se dejó a temperatura ambiente a lo largo del fin de semana. La mezcla de reacción se vertió en una mezcla de HCl aq. diluido y EtOAc. La capa orgánica se separó, se secó y evaporó para dar un sólido que se trituró con éter para dar el compuesto del título en forma de un sólido blanco (7,7 g).
- 10 δ H (400 MHz, d_6 -DMSO) 1,00 (3H, t), 1,67-1,87 (2H, m), 4,10 (2H, t), 7,24 (1H, d), 7,84-8,06 (2H, m), 12,97 (1H, s ancho). MS (ES) $C_{10}H_{11}^{35}ClO_3$ requiere 214; encontrado 213 ($M-H^+$).

Descripción para D101

- 15 **3-(3-Cloro-5-{5-[3-cloro-4-(propiloxi)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de etilo (D101)**



- Ácido 3-cloro-4-(propiloxi)benzoico (**D100**) (150mg, 0,70 mmol) agitado en DMF se trató con EDC (146mg, 0,76 mmol) seguido de HOBt (104mg, 0,76 mmol). La disolución resultante se agitó y se añadió 3-{3-cloro-5-[(hidroxiamino)(imino)metil]-1H-indol-1-il}propanoato de etilo (**D96**) (216mg, 0,70 mmol). La mezcla se calentó a 80 °C hasta que la reacción fue completa. El tratamiento posterior proporcionó el compuesto del título en forma de 160 mg de sólido de color crema pálido. δ H (400
- 20

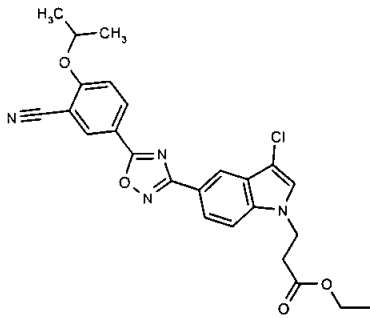
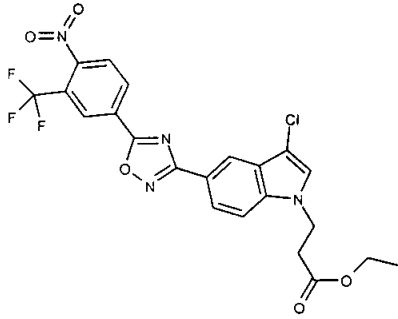
MHz, d_6 -DMSO) 1,03 (3H, t), 1,10 (3H, t), 1,77-1,86 (2H, m), 2,90 (2H, t), 4,05 (2H, q), 4,18 (2H, t), 4,49 (2H, t), 7,40 (1H, d), 7,74 (1H, s), 7,81 (1H, d), 7,91 (1H, dd), 8,15 (1H, dd), 8,22-8,23 (2H, m). MS (ES) $C_{24}H_{23}^{35}Cl_2N_3O_4$ requiere 487; encontrado 488 (MH^+).

5

Los siguientes compuestos se prepararon por métodos similares a los descritos anteriormente. Las reacciones trataron posteriormente repartiendo el material bruto entre acetato de etilo y bicarbonato de sodio aq., separando la capa orgánica, secándola y evaporando hasta sequedad. Los compuestos se purificaron por trituración o cromatografía en una fase normal.

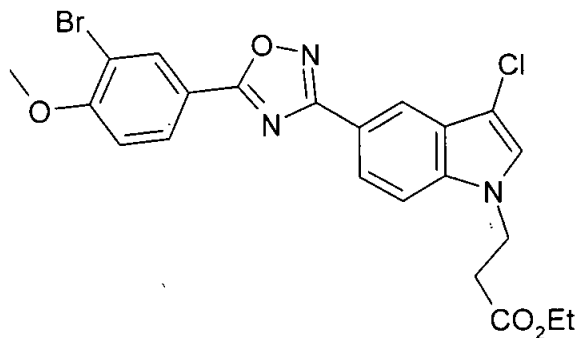
10

	Estructura	precursor	Nombre	MH^+
D102		D96	3-(3-cloro-5-{5-[3-cloro-4-(metiloxi)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de etilo	460
D103		D96	3-(3-cloro-5-{5-[4-(trifluorometil)-3-(metiloxi)-1,2,4-oxadiazol-3-il]-1H-indol-1-il)propanoato de etilo	494

D104		D96	3-[3-cloro-5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoato de etilo	479
D105		D96	3-(3-cloro-5-{5-[4-nitro-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de etilo	-

Descripción para D106

3-(5-{5-[3-Bromo-4-(metiloxi)fenil]-1,2,4-oxadiazol-3-il}-3-cloro-1H-indol-1-il)propanoato de etilo (D106)



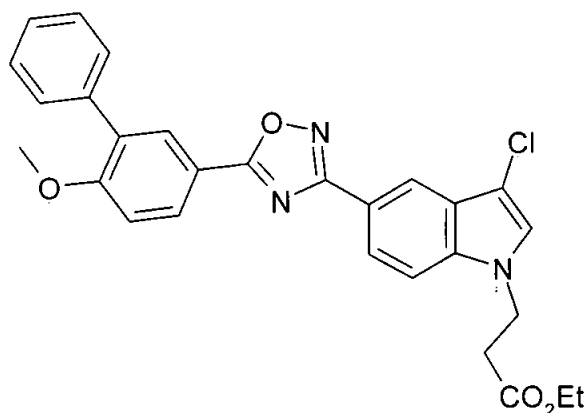
5

El ácido 3-bromo-4-(metiloxi)benzoico (comercial: ICN) (243mg, 1,05 mmol) agitando en DMF (10ml) se trató con EDC (219mg, 0.1.14 mmol) seguido de HOBt (156mg, 0.1.14 mmol). La disolución resultante se agitó durante 10 minutos. Se

añadió 3-{3-cloro-5-[(hidroxiamino)(imino)metil]-1H-indol-1-il}propanoato de etilo (D96) (324mg, 1,05 mmol) y se agitó a TA durante 45 minutos. La disolución se calentó a 80 °C durante 4 horas y después se dejó estar durante una noche. La disolución se calentó a 80 °C durante otras 4 horas para dar un producto mayoritario. Se separó la DMF por evaporación, se añadió EtOAc (50ml) y se lavó con agua (50ml). El EtOAc se lavó con una disolución acuosa sat. de hidrogenocarbonato sódico (50 ml) y agua (50 x ml) y después se secó sobre MgSO₄. Se separó el disolvente por evaporación y se recristalizó en etanol para dar el compuesto del título como 280mg de sólido de color crema. δ H (400 MHz, d₆-DMSO) 1,10 (3H, t), 2,90 (2H, t), 3,99-4,05 (5H, m), 4,49 (2H, t), 7,38 (1H, d), 7,74 (1H, s), 7,80 (1H, d), 7,97 (1H, d), 8,21-8,23 (2H, m), 8,36 (1H, d). MS (ES) C₂₂H₁₉⁸¹Br³⁵ClN₃O₄ requiere 505; encontrado 506 (MH⁺).

Descripción para D107

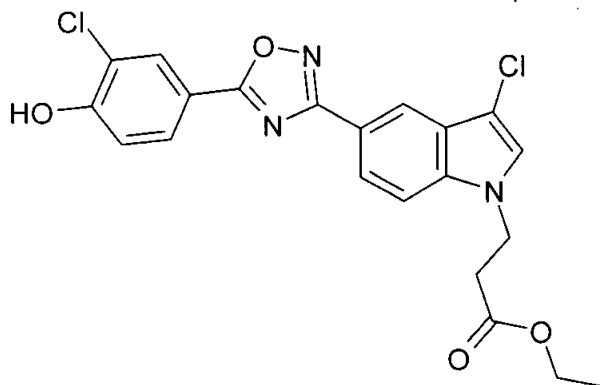
15 3-(3-Cloro-5-{5-[6-(metiloxi)-3-bifenilil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de etilo (D107)



3-(5-{5-[3-bromo-4-(metiloxi)fenil]-1,2,4-oxadiazol-3-il}-3-cloro-1H-indol-1-il)propanoato de etilo (D106) (212mg, 0,42 mmol), ácido fenilborónico (104mg, 0,84 mmol), Pd(PPh₃)₄ (20mg) y disolución aq. 2N de carbonato de sodio (3ml, 6mmol) se suspendieron in DME (6ml) y se calentó a 90 °C durante 2 horas. Se añadió ácido fenilborónico (30mg, 0,24 mmol) y Pd(PPh₃)₄ (20mg) y se calentó a 90 °C durante otras 2 horas. Se añadió EtOAc (70ml) y se lavó con agua (100ml). Se secó sobre MgSO₄ y el disolvente se separó por evaporación. El residuo se cristalizó en etanol para dar 90 mg del compuesto del título en forma de un sólido de color canela claro. MS (ES) C₂₈H₂₄³⁵ClN₃O₄ requiere 501; encontrado 502 (MH⁺).

Descripción para D108

3-{3-Cloro-5-[5-(3-cloro-4-hidroxifenil)-1,2,4-oxadiazol-3-il]-1*H*-indol-1-il}propanoato de etilo (D108)

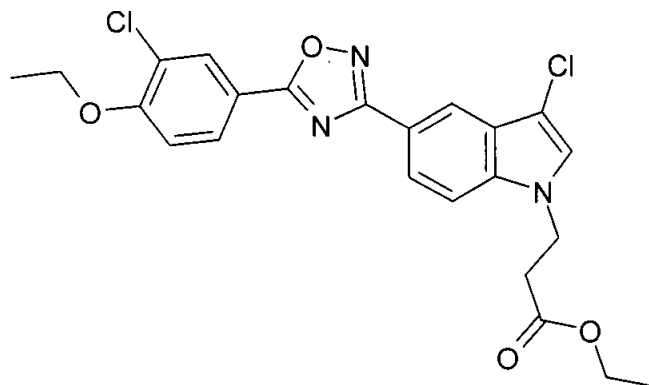


- 5 Ácido 3-cloro-4-hidroxibenzoico (comercial) (240mg, 1,40 mmol) en DMF seca (8ml) se trató con EDC (292mg, 1,52 mmol) y HOBt (208mg, 1,52 mmol) y se agitó durante 5 minutos. Se añadió 3-{3-cloro-5-[(hidroxiamino)(imino)metil]-1*H*-indol-1-il}propanoato de etilo (**D96**) (432mg, 1,40 mmol) y se agitó a TA durante 30 minutos. La mezcla de reacción se calentó a 80°C durante 7 horas. Se añadió EtOAc (70ml) y
- 10 se lavó con agua (70ml), hidrógeno-carbonato de sodio acuoso saturado (70ml) y agua (70ml). Se secó sobre MgSO₄ y el disolvente se separó por evaporación. El residuo se sometió a cromatografía usando un Biotage (EtOAc/hexano 1:2) para obtener el compuesto del título como 200mg de sólido blanco. δ H (400 MHz, d₆-DMSO) 1,10 (3H, t), 2,91 (2H, t), 4,04 (2H, q), 4,50 (2H, t), 7,67-7,70 (2H, m), 7,75
- 15 (1H, s), 7,80-7,81 (2H, m), 7,94 (1H, dd), 8,22-8,25 (1H, m), 10,95 (1H, s ancho). MS (ES) C₂₁H₁₇³⁵Cl₂N₃O₄ requiere 445; encontrado 446 (MH⁺).

Descripción para D109

3-{3-Cloro-5-[5-[3-cloro-4-(etiloxi)fenil]-1,2,4-oxadiazol-3-il]-1*H*-indol-1-il}propanoato de etilo (D109)

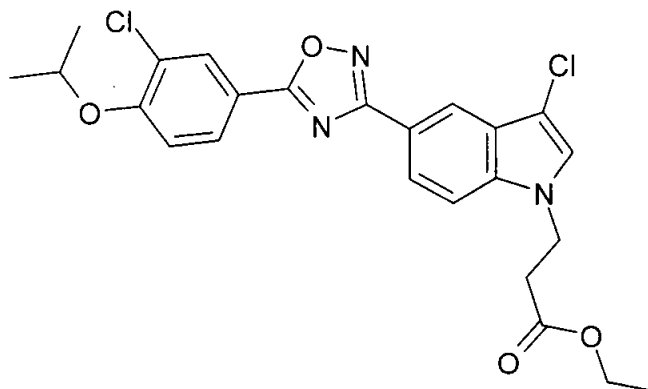
20



A 3-[3-cloro-5-[5-(3-cloro-4-hidroxifenil)-1,2,4-oxadiazol-3-il]-1*H*-indol-1-il]propanoato de etilo (**D108**) (180mg, 0,40 mmol) y K₂CO₃ (138mg, 1,0 mmol) en DMF seca (3ml) se añadió yoduro de etilo (78mg, 0,50 mmol) y la mezcla se calentó a 80 °C con agitación durante 30 minutos. Se enfrió la mezcla y se añadió EtOAc (50ml). Se lavó con agua (3x40ml) y se secó sobre MgSO₄. Se separó el disolvente por evaporación y se recrystalizó en etanol para dar el compuesto del título como 110mg de sólido de color blanco. δ H (400 MHz, d₆-DMSO) 1,10 (3H, t), 1,42 (3H, t), 2,90 (2H, t), 4,02 (2H, q), 4,27 (2H, q), 4,49 (2H, t), 7,40 (1H, d), 7,74 (1H, s), 7,80 (1H, d), 7,95 (1H, dd), 8,16 (1H, dd), 8,21-8,22 (2H, m). MS (ES) C₂₃H₂₁³⁵Cl₂N₃O₄ requiere 473; encontrado 474 (MH⁺).

Descripción para D110

3-[3-Cloro-5-(5-[3-cloro-4-[(1-metiletil)oxi]fenil)-1,2,4-oxadiazol-3-il)-1*H*-indol-1-il]propanoato de etilo (**D110**)

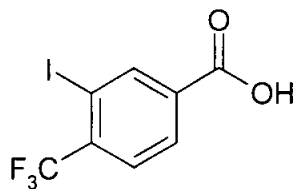


A 3-[3-cloro-5-[5-(3-cloro-4-hidroxifenil)-1,2,4-oxadiazol-3-il]-1*H*-indol-1-il]propanoato de etilo (**D108**) (180mg, 0,40 mmol) y K₂CO₃ (138mg, 1,0 mmol) en DMF seca (5ml) se añadió yoduro de isopropilo (85mg, 0,50 mmol) y la mezcla se agitó a 80 °C durante 30 minutos. Se enfrió la mezcla y se añadió EtOAc (50ml). Se

lavó con agua (2X50ml) y se secó sobre MgSO_4 . Se separó el disolvente por evaporación y se recrystalizó en etanol para dar el compuesto del título como 120mg de sólido de color blanco. δH (400 MHz, d_6 -DMSO) 1,12 (3H, t), 1,37 (6H, d), 2,91 (2H, t), 4,02 (2H, q), 4,50 (2H, t), 4,89-4,98 (1H, m), 7,72-7,85 (5H, m), 7,95-8,00 (1H, m), 8,24 (1H, d). MS (ES) $\text{C}_{24}\text{H}_{23}^{35}\text{Cl}_2\text{N}_3\text{O}_4$ requiere 487; encontrado 488 (MH^+).

Descripción para D111

Ácido 3-yodo-4-(trifluorometil)benzoico (D111)



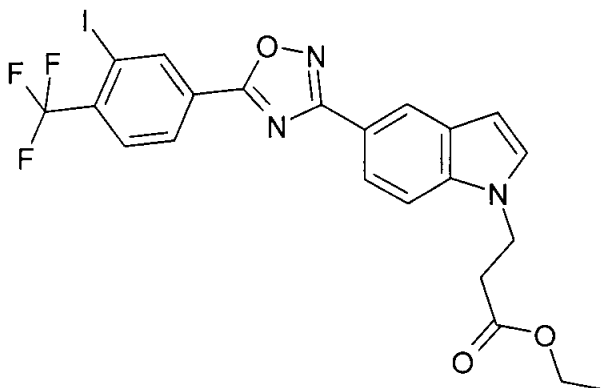
10 Ácido 3-amino-4-(trifluorometil)benzoico (disponible en el mercado) (6,5 g, 31,7 mmol) y triyodometano (37,4 g, 95,1 mmol) se disolvieron en THF (300 ml). La mezcla de reacción se calentó a 80 °C y después se añadió lentamente (5,56 ml, 47,6 mmol) a esta temperatura. Se continuó calentando a esta temperatura durante 4 horas y después la reacción se concentró a *vacío* para dar el producto bruto. Se

15 purificó por cromatografía en columna (de hexano a 30% de EtOAc en hexano). Este material se combinó con otro lote de una reacción similar realizada con 2 g de ácido 3-amino-4-(trifluorometil)benzoico. El material combinado se purificó por HPLC preparativa para dar el compuesto del título (6,1 g). MS $\text{C}_8\text{H}_4\text{F}_3\text{IO}_2$ requiere 316; encontrado 315 (M-H^+).

20

Descripción para D112

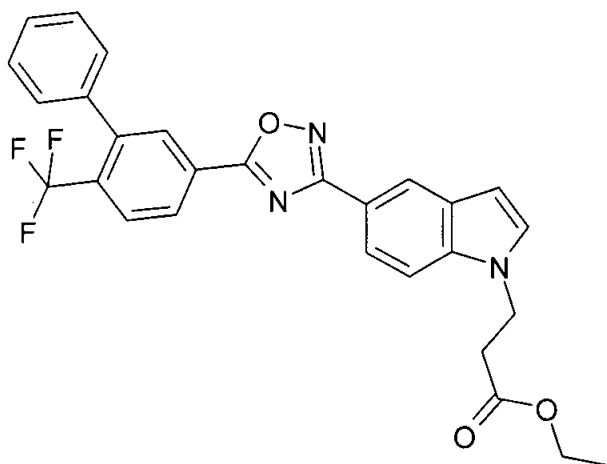
3-(5-{5-[3-Yodo-4-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de etilo (D112)



D111 (1,0 g, 3,16 mmol) se disolvió en DMF (25 ml) en atmósfera de nitrógeno. Se añadieron EDC (0,7 g, 3,7 mmol) y HOBt (0,5 g). La reacción se agitó a temperatura ambiente durante 15 minutos y después se añadió trietilamina (0,87 ml, 6,32 mmol) y la reacción se agitó durante otros 5 minutos. Se añadió **D52** (0,87 g, 3,16 mmol) y la reacción se agitó a temperatura ambiente durante una noche. La reacción se concentró *a vacío* y el aceite resultante se diluyó con acetato de etilo (100 ml). La capa orgánica se lavó con agua (2 x 30 ml), se secó (Na_2SO_4) y concentró *a vacío* para dar el producto bruto que se purificó por cromatografía en columna. El producto se eluyó con 7% de EtOAc en hexano y la evaporación proporcionó el compuesto del título (0,45 g). MS $\text{C}_{22}\text{H}_{17}\text{F}_3\text{IN}_3\text{O}_3$ requiere 555; encontrado 556 (MH^+).

Descripción para D113

3-(5-{5-[6-(Trifluorometil)-3-bifenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de etilo (D113)

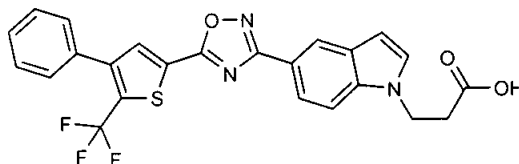


Este material se preparó por un método similar al usado para **D107** a partir de **D112**. MS (ES) $\text{C}_{28}\text{H}_{22}\text{F}_3\text{N}_3\text{O}_2$ requiere 505; encontrado 506 (MH^+).

Ejemplos

Ejemplo 1

Ácido 3-(5-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico (E1)

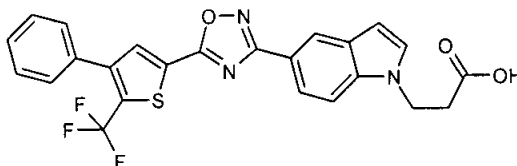


- D3 (38 mg) se disolvió en NaOH acuoso 2M (0,5 ml) y MeOH (0,5 ml) después se agitó a TA durante una noche. El análisis LCMS indicó 41% de producto, así que la mezcla de reacción se calentó a 50 °C y se agitó a lo largo del fin de semana. La LCMS mostró que la reacción era completa. La mezcla de reacción se evaporó y después se repartió entre H₂O y DCM. La capa orgánica se extrajo con H₂O. Los extractos acuosos combinados se acidularon hasta pH = 1 y se extrajeron con DCM. Estos extractos en DCM se secaron sobre MgSO₄, se filtraron y se evaporaron para dar el producto deseado (30 mg). El producto bruto se purificó sobre un cartucho de sílice (12+S), eluyendo con una mezcla de 0 a 10 % de MeOH en DCM para dar el producto purificado. Este se disolvió en CHCl₃ y evaporó para dar el compuesto del título (3 mg) en forma de un sólido blanco. δ H (CDCl₃, 400MHz): 2,92 (2H, t), 4,50 (2H, t), 6,51 (1H, d), 7,24 (1H, d), 7,40-7,53 (6H, m), 7,90 (1H, s), 8,00 (1H, d), 8,45 (1H, s). EM (ES⁺): C₂₄H₁₆F₃N₃O₃S requiere 483; encontrado 484 (MH⁺).

15

Ejemplo 1 (procedimiento alternativo)

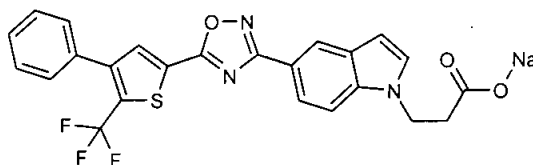
Ácido 3-(5-(5-(4-phenyl-5-(trifluoromethyl)-2-thienyl)-1,2,4-oxadiazol-3-yl)-1H-indol-1-yl)propanoico (E1)



- D3 (600 mg) se trató con NaOH 2 M aq. (25 ml) y MeOH (25 ml). Esta mezcla se agitó durante una noche y después se calentó a 50 °C durante 6 horas. El MeOH después se evaporó y la solución restante se aciduló y extrajo con EtOAc (x 3). Las disoluciones orgánicas combinadas se lavaron con salmuera y evaporaron para dar el residuo bruto C(302 mg) en forma de un sólido blanquecino. Este se trituró con MeOH frío para dar el compuesto del título (162 mg) en forma de un sólido gris. δ H (d₆-DMSO, 400MHz): 2,80 (2H, t), 4,46 (2H, t), 6,64 (1H, d), 7,49-7,59 (6H, m), 7,72 (1H, d), 7,85 (1H, dd), 8,22-8,25 (1H, m), 8,31-8,34 (1H, m). MS (ES): C₂₄H₁₆F₃N₃O₃S requiere 483; encontrado 484 (MH⁺).

Ejemplo 2:

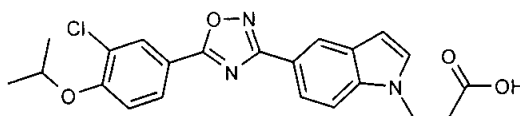
3-(5-{5-[4-Fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1*H*-indol-1-il)propanoato de sodio (E2)



- 5 **E1** (30 mg) se disolvió en EtOAc (1 ml), se trató con NaOH acuoso 2M (40 ul), se diluyó con H₂O (1 ml) y se extrajo con EtOAc (3 x 5 ml), usando un pequeño volumen de salmuera durante la tercera extracción para facilitar la separación de fases. Los extractos orgánicos combinados se evaporaron para dar el compuesto del título (37 mg) como un sólido verde. δ H (metanol-d₄, 400MHz): 2,68 (2H, t), 4,48 (2H, t), 6,55 (1H, d), 7,49 (1H, d), 7,45-7,56 (5H, m), 7,62 (1H, d), 7,92 (1H, d), 8,03 (1H, s), 8,35 (1H, s). EM (ES⁺): C₂₄H₁₆F₃N₃O₃S requiere 483; encontrado 484 (MH⁺).
- 10

Ejemplo 3

Ácido 3-[5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1*H*-indol-1-il]propanoico (E3)

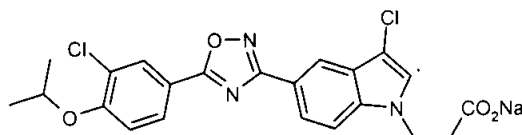


- D6** MF105672-178A2 (38 mg) se disolvió en EtOH, se trató con solución acuosa de NaOH 12,5 M (2 ml) y se agitó a TA durante 4 horas. La mezcla de reacción se evaporó, re-disolvió en H₂O y se lavó con dietil éter. La solución acuosa se aciduló y se extrajo con DCM. Las soluciones en DCM se combinaron, se secaron sobre MgSO₄, filtraron y evaporaron para dar el compuesto del título MF105672-181A1 (5 mg) como un sólido amarillo pálido. δ H (CDCl₃, 400MHz): 1,44 (6H, d), 2,94 (2H, t), 4,51 (2H, t), 4,73 (1H, septete), 6,61 (1H, d), 7,07 (1H, d), 7,22 (1H, d), 7,45 (1H, d), 7,94 (1H, d), 8,07 (1H, d), 8,27 (1H, s), 8,47 (1H, s). MS (ES): C₂₂H₂₀ClN₃O₄ requiere 425; encontrado 426 (MH⁺).
- 20
- 25

Ejemplo 4

3-[3-Cloro-5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1*H*-indol-1-il]propanoato de sodio (E4)

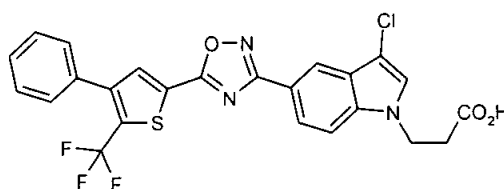
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D7 (200 mg) y Cs_2CO_3 (336 mg) se pusieron en un vial de microondas, se trataron con DMF (2,8 ml) y 3-bromopropionato de etilo (99 μl) y sonicaron durante 10 minutos. La mezcla después se calentó a 120 °C en un reactor de microondas durante 25 mins. Después, la mezcla de reacción se evaporó, re-disolvió en MeOH (10 ml) y se trató con NaOH aq. 2 M (10 ml). Esta mezcla se sonicó brevemente y después se calentó a 50 °C durante una noche. Después, la mezcla de reacción se evaporó, se diluyó con H_2O (70 ml) y extrajo con EtOAc, añadiendo NaCl y acetona para mejorar la extracción. Los extractos orgánicos se evaporaron para dar el producto bruto que se aciduló con HCl para dar el ácido libre. Este era insuficientemente soluble para purificarlo por cromatografía, así que se trituró con MeOH, se trató con NaOH ac. 2M (1,5 eq.), se evaporó, disolvió en EtOAc, filtró y evaporó para dar el compuesto del título (56 mg) en forma de un sólido pardo. δH (metanol- d_4 , 400MHz): 1,42 (6H, d), 2,66 (2H, t), 4,47 (2H, t), 4,82 (1H, m), 7,29 (1H, d), 7,44 (1H, s), 7,65 (1H, d), 7,98 (1H, d), 8,12 (1H, d), 8,20 (1H, s), 8,30 (1H, s). MS (ES): $\text{C}_{22}\text{H}_{19}^{35}\text{Cl}_2\text{N}_3\text{O}_4$ requiere 459; encontrado 460 (MH^+).

Ejemplo 5

20 **Ácido 3-(3-cloro-5-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico (E5)**



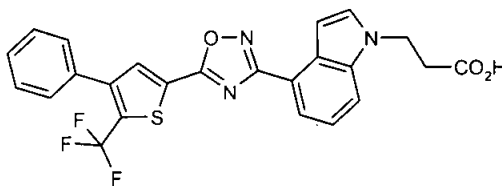
D8 (86 mg), 3-bromopropionato (52 mg), Cs_2CO_3 (126 mg) y DMF (1 ml) se pusieron en un vial de microondas y se agitó a 131 °C en el reactor de microondas durante 1,5 horas. Después, la mezcla de reacción se evaporó hasta sequedad y se trató con NaOH ac. 2M y EtOH (20 ml). Esta disolución se agitó a 50 °C durante 4 horas y después se neutralizó con HCl y evaporó para separar el EtOH. Después la solución acuosa se extrajo dos veces con EtOAc y los extractos orgánicos combinados se evaporaron. El residuo se disolvió en DMSO, filtró, se trató con MeCN causando precipitación del producto que se filtró y se lavó con MeCN para dar el compuesto

del título (23 mg) en forma de un sólido blanquecino. δ H (d_6 -DMSO, 400MHz): 2,47-2,57 (disolvente + 2H), 4,37 (2H, t), 7,51-7,59 (5H, m), 7,72 (1H, s), 7,76 (1H, d), 7,89 (1H, d), 8,17 (1H, s), 8,25 (1H, s). MS (ES): $C_{24}H_{15}ClF_3N_3O_2S$ requiere 517; encontrado 516 ($M-H^+$).

5

Ejemplo 6

Ácido 3-(4-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico (E6)

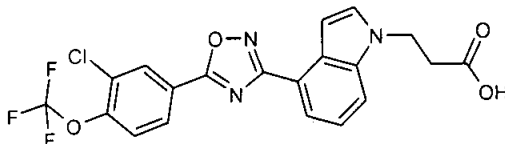


- 10 **D10** (85 mg, 0,207 mmol) se puso en un vial de microondas con Cs_2CO_3 (135 mg) y DMF (1 ml). Este se agitó brevemente y se añadió bromopropionate de etilo (40 μ l). La mezcla se calentó a 130 °C durante 1,5 horas en el reactor de microondas. La mezcla de reacción se transfirió a un matraz que contenía NaOH acuoso 2 M (5 ml) y EtOH (5 ml), y después se agitó a temperatura ambiente durante una noche.
- 15 Después la mezcla se evaporó y el residuo se aciduló a pH = 2,5 con HCl acuoso 2 M. Esta disolución se extrajo con EtOAc dos veces y los extractos combinados se evaporaron para dar un residuo amarillo que se purificó por MDAP para dar el compuesto del título (50 mg) en forma de un sólido blanco. δ H ($CDCl_3$, 400MHz): 2,93 (2H, t), 4,50 (2H, t), 7,26 (1H, s), 7,33 (1H, d), 7,37 (1H, ap t), 7,45-7,52 (5H, m), 7,55 (1H, d), 7,93 (1H, s), 8,04 (1H, d). MS (ES): $C_{24}H_{16}F_3N_3O_3S$ requiere 483;
- 20 encontrado 482 ($M-H^+$).

Ejemplo 7

Ácido 3-[4-(5-{3-cloro-4-[(trifluorometil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoico (E7)

25



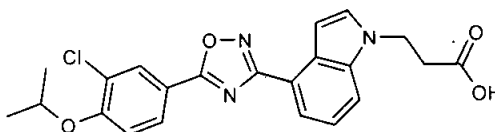
Ácido 3-cloro-4-[(trifluorometil)oxi]benzoico (fuente comercial) (131 mg), EDCI (114 mg) y HOBT (81 mg) se disolvieron en DMF (2,5 ml) y se agitaron a TA durante 10 minutos. Se añadió 3-{5-[(hidroxiamino)(imino)metil]-1H-indol-1-il}propanoato de etilo

286
252

(D57) (150 mg) en DMF (2,5 ml) y se continuó agitando a TA durante 2 horas. Después se calentó la mezcla a 80 °C durante la noche. La mezcla de reacción se evaporó hasta sequedad y después se extrajo con EtOAc (2 x 25 ml) de H₂O (25 ml). Las disoluciones orgánicas combinadas se evaporaron hasta sequedad y el residuo se trató con EtOH y NaOH aq. 2 M (mezcla 1:1, 20 ml). Esta mezcla se agitó a 50 °C durante 2 horas, después se evaporó para separar el EtOH. El precipitado resultante se separó por filtración y se lavó con una mezcla de H₂O y EtOH y después con HCl 2 M. El residuo se recrystalizó en EtOH para dar el compuesto del título (62 mg) en forma de un sólido blanco. δ H (d₆-DMSO, 400MHz): 2,81 (2H, t), 4,50 (2H, t), 7,08 (1H, d), 7,36 (1H, t aparente), 7,61 (1H, d), 7,83 (1H, d), 7,89 (1H, d), 7,96 (1H, d), 8,32 (1H, dd), 8,50 (1H, d). MS (ES⁻): C₂₀H₁₃³⁵ClF₃N₃O₄ requiere 451; encontrado 450 (M-H⁺).

Ejemplo 8

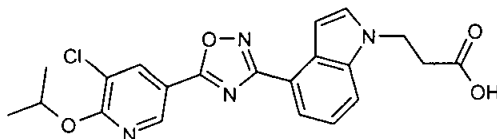
15 **Ácido 3-[4-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoico (E8)**



Ácido 3-cloro-4-[(1-metiletil)oxi]benzoico (D4) (117 mg) se añadió a EDCI (114 mg) y HOBT (81 mg) se disolvió en DMF (2,5 ml). Este se agitó a TA durante 10 minutos y después se añadió 3-{4-[(hidroxiamino)(imino)metil]-1H-indol-1-il}propanoato de etilo (D57) (150 mg) en DMF (2,5 ml) y se continuó agitando a TA durante 2 horas y después a 80 °C durante una noche. La mezcla de reacción se evaporó hasta sequedad y después se extrajo del agua con EtOAc (2 x 25 ml) de H₂O (25 ml). Los extractos orgánicos combinados se evaporaron y se trataron con NaOH aq. 2 M (10 ml) y EtOH (10 ml), se agitó a 50 °C durante 2 horas, y después se evaporó para separar el EtOH. La solución residual se aciduló, filtró y el precipitado se lavó con EtO/H₂O y después se recrystalizó en EtOH/H₂O en caliente y después en DMSO. El lavado con Et₂O y MeOH dio el compuesto del título (46 mg) en forma de un sólido blanco. δ H (d₆-DMSO, 400MHz): 1,37 (6H, d), 2,81 (2H, t), 4,50 (2H, t), 4,89 (1H, septete), 7,08 (1H, d), 7,35 (1H, t aparente), 7,46 (1H, d), 7,60 (1H, d), 7,81 (1H, d), 7,94 (1H, d), 8,15 (1H, dd), 8,23 (1H, d). MS (ES⁻): C₂₂H₂₀³⁵ClN₃O₄ requiere 425; encontrado 424 (M-H⁺).

Ejemplo 9

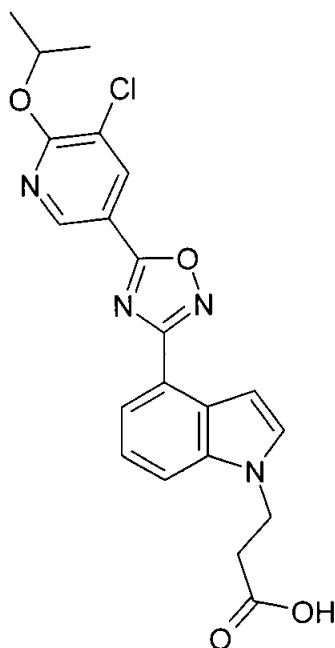
Ácido 3-[4-(5-{5-cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoico (E9)



- 5 3-{4-[(hidroxiamino)(imino)metil]-1H-indol-1-il}propanoato de etilo (**D57**) (150 mg) en DMF (2,5 ml) se añadió a una disolución de ácido 5-cloro-6-[(1-metiletil)oxi]-3-piridinacarboxílico (**D61**) (118 mg), HOBT (81 mg) y EDCI (114 mg) que se había estado agitando a TA durante 10 minutos en DMF (2,5 ml). La mezcla resultante se agitó a TA durante 2 horas y después se calentó a 80 °C durante tres días. La
- 10 mezcla de reacción se evaporó hasta sequedad y después se extrajo del agua con EtOAc (2 x 25 ml) de H₂O (25 ml). Los extractos orgánicos combinados se evaporaron y el residuo se agitó en EtOH/NaOH aq. 2 M (mezcla 1:1, 20 ml) a 50 °C durante 2 horas. El EtOH se evaporó y el precipitado se separó por filtración. Este se aciduló y después se purificó por MDAP para dar el compuesto del título (48 mg) en
- 15 forma de un sólido blanquecino. δ H (d_6 -DMSO, 400MHz): 1,40 (6H, d), 2,80 (2H, t), 4,50 (2H, t), 5,46 (1H, septete), 7,08 (1H, d), 7,36 (1H, t aparente), 7,60 (1H, d), 7,82 (1H, d), 7,95 (1H, d), 8,60 (1H, d), 8,97 (1H, d). MS (ES⁻): C₂₁H₁₉³⁵ClN₄O₄ requiere 426; encontrado 425 (M-H⁺).

20 **Ejemplo 9 (procedimiento alternativo)**

Ácido 3-[4-(5-{5-cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoico (E9)



3-[4-(5-(5-chloro-6-((1-metiletil)oxi)-3-piridinil)-1,2,4-oxadiazol-3-il)-1H-indol-1-

il]propanoato de etilo (**D62**) (1,1 g, 2,418 mmol) se disolvió en una mezcla de 1,4-dioxano (100 ml) y etanol (100 ml). Se añadió agua (50,0 ml) seguida de hidróxido

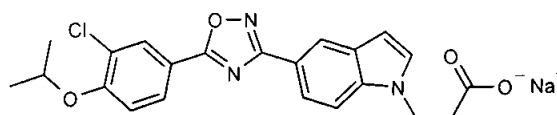
5 de sodio 2N (2,418 ml, 4,84 mmol). La mezcla se agitó a TA durante una hora y media para dar un solo producto. Se evaporó la mayor parte del disolvente, se aciduló con ácido acético glacial, se añadió agua (50ml) y el producto se extrajo en EtOAc (200ml). Se lavó con agua (30ml) y se secó sobre MgSO₄. El disolvente se separó por evaporación hasta que se formó un precipitado blanco. El sólido se

10 separó por filtración y se lavó con éter. La masa de compuesto del título obtenida fue de 780mg. δ H (400 MHz, d₆-DMSO) 1,38 (6H, d), 2,81 (2H, t), 4,50 (2H, t), 5,41-5,51 (1H, m), 7,07 (1H, dd), 7,36 (1H, t), 7,59 (1H, d), 7,81 (1H, d), 7,94 (1H, dd), 8,58 (1H, d), 8,96 (1H, d), 12,40 (1H, s ancho). MS (ES) C₂₁H₁₉³⁵ClN₄O₄ requiere 426; encontrado 427 (MH⁺).

15

Ejemplo 10

3-[5-(5-[3-Cloro-4-[(1-metiletil)oxi]fenil]-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoato de sodio (**E10**)



20

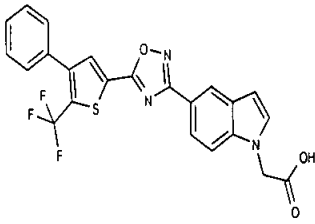
(D5) (200 mg) se disolvió en DMF (4 ml), se trató con Cs_2CO_3 (368 mg) y después con bromopropionato de etilo (109 μl). La mezcla resultante se calentó a 120 °C en un reactor de microondas durante 2 horas. La mezcla de reacción se decantó del residuo insoluble y se evaporó hasta sequedad para dar un aceite anaranjado pálido.

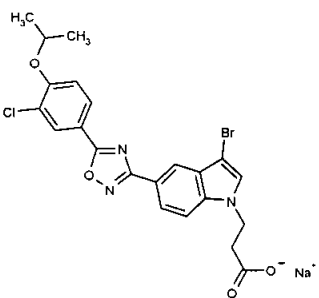
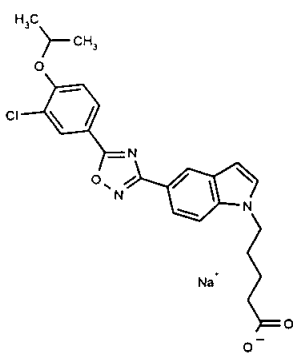
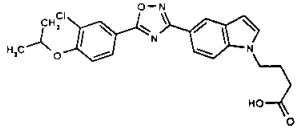
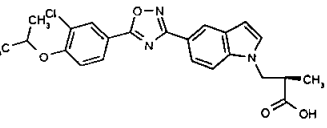
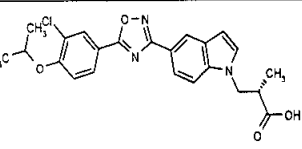
Este aceite se disolvió en EtOH (2 ml) y se trató con NaOH acuoso 2 M (2 ml). Esto produjo un precipitado blanco, así que se añadió otra porción de EtOH (2 ml) para producir una disolución homogénea. La mezcla resultante se calentó a 60 °C durante 1 hora y después se dejó estar a TA durante una noche. La mezcla de reacción se evaporó hasta sequedad, re-disolvió en H_2O (10 ml), se trató con salmuera (2 ml) y extrajo con una mezcla de EtOAc y MeCN (2 x 20 ml). La evaporación dio el producto bruto (313 mg) como un sólido verde pálido. Este se disolvió en MeOH (5 ml), filtró y evaporó y después se trituroó con Et_2O para dar el compuesto del título (247 mg) como un sólido verde pálido. δH (metanol- d_4 , 400MHz): 1,42 (6H, d), 2,68 (2H, t), 4,48 (2H, t), 4,83 (1H, septete), 6,55 (1H, dd), 7,30 (1H, d), 7,38 (1H, d), 7,61 (1H, d), 7,91 (1H, dd), 8,12 (1H, dd), 8,21 (1H, d), 8,34 (1H, dd). MS (ES-): $\text{C}_{22}\text{H}_{20}\text{ClN}_3\text{O}_4$ requiere 425 encontrado 424 ($\text{M}-\text{H}^+$).

Los siguientes compuestos se prepararon de una manera similar a la del Ejemplo 1:

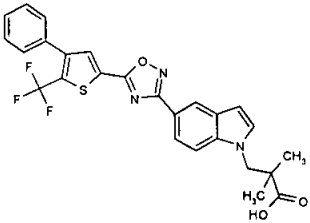
El disolvente para la etapa de hidrólisis fue o bien metanol o etanol y la temperatura de reacción entre temperatura ambiente y 60 °C. En algunos casos, las reacciones se trataron extrayendo el producto o el producto acidulado en un disolvente orgánico y en otros casos el compuesto final precipitó de la capa acuosa y se aisló por filtración. La purificación se hizo por MDAP, trituración o recristalización.

25

Ejemplo	Estructura	Nombre	Comentarios	MS
E11		Ácido (5-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)acético	Hidrólisis de D42	470 (MH^+)

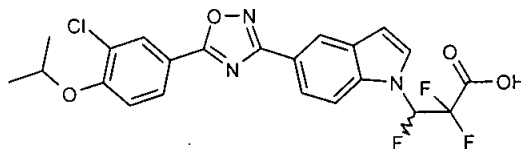
E12		3-[3-bromo-5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoato de sodio	Hidrólisis de D43	504 (M-H ⁺ para ³⁵ Cl & ⁸¹ Br)
E13		5-[5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]pentanoato de sodio	Hidrólisis de D44	454 (MH ⁺ para ³⁵ Cl)
E14		Ácido 4-[5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoico	Hidrólisis de D45	440 (MH ⁺ para ³⁵ Cl)
E15		Ácido (2R)-3-[5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]-2-metilpropanoico	Hidrólisis de D46	440 (MH ⁺ para ³⁵ Cl)
E16		Ácido (2S)-3-[5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]-2-metilpropanoico	Hidrólisis de D47	440 (MH ⁺ para ³⁵ Cl)

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E17		Ácido 2,2-dimetil-3-(5-{4-fenil-5-(trifluorometil)-2-tienil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il)propanoico	Hidrólisis de D48.	512 (MH ⁺)
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Ejemplo 18

Ácido 3-[5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]-2,2,3-trifluoropropanoico (E18)



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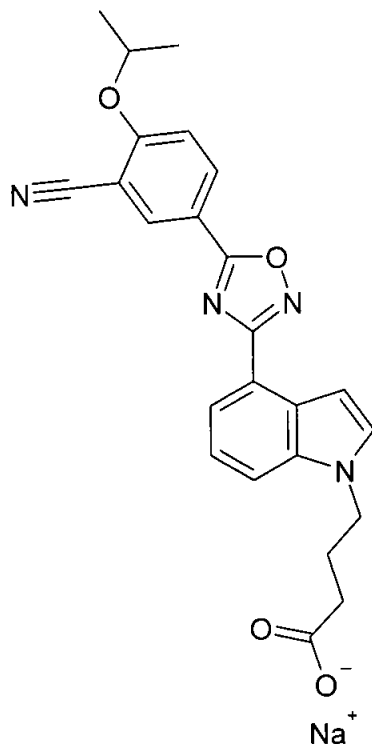
D5 (200 mg), Cs₂CO₃ (552 mg) y DMF (2,8 ml) se agitaron a TA y se trataron con ácido 3-bromo-2,2,3-trifluoropropanoico (175 mg). Esta mezcla se calentó a 140 °C durante 1 hora en un reactor de microondas. Se añadieron 2 equivalente más de Cs₂CO₃ (368 mg) y se continuó calentando a 140 °C durante 10 horas. Después, la mezcla de reacción se evaporó, se trató con H₂O₂, se sacudió y filtró para dar un residuo sólido marrón. Éste se purificó por MDAP para producir el compuesto del título en forma de un sólido blanco (12 mg). δH (metanol-d₄, 400MHz): 1,42 (6H, d), 4,83 (1H, septete), 6,87 (1H, d), 7,29 (1H, d), 7,45 (1H, d), 7,54 (1H, d), 7,61 (1H, d), 7,80 (1H, d), 8,06 (1H, d), 8,11 (1H, d), 8,19-8,22 (1H, m), 8,44 (1H, s).

15

Ejemplo 19

4-[4-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoato de sodio (E19)

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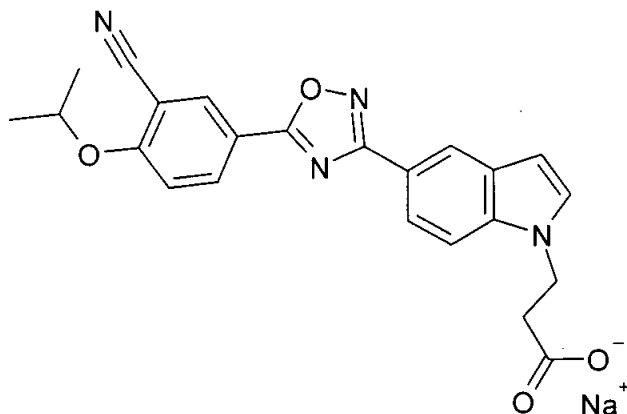


A una disolución de 4-[4-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoato de etilo (**D65**) (1,42g, 3,09 mmol) en una mezcla de dioxano
5 (70ml) y etanol (70ml) se trató con hidróxido de sodio 2N (1,86ml, 3,71 mmol) seguido de agua (35ml). La disolución se agitó a TA durante 4 horas. Se evaporó la mayor parte del disolvente y se separó por filtración el sólido blanco del disolvente restante. El sólido se lavó con agua seguida de éter y se secó para dar 580mg del compuesto del título. δ H (400 MHz, metanol- d_4) 1,45 (6H, d), 2,09-2,22 (4H, m), 4,30
10 (2H, t), 4,92-4,98 (1H, m), 7,15 (1H, d), 7,31 (1H, t), 7,38-7,43 (2H, m), 7,69 (1H, d), 7,95 (1H, d), 8,43-8,46 (2H, m). MS (ES) $C_{24}H_{22}N_4O_4$ requiere 430; encontrado 431 (MH^+).

Ejemplo 20:

15 **3-[5-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoato de sodio**

259

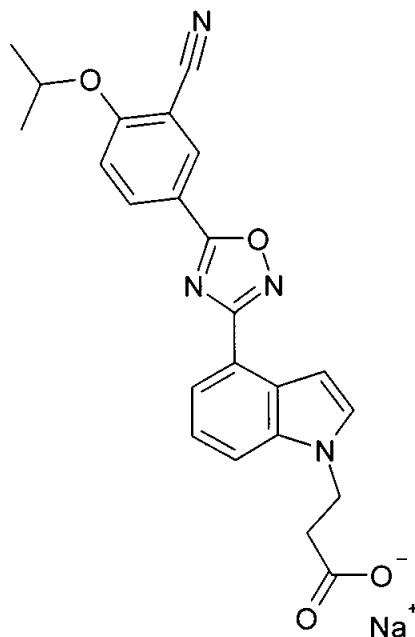


3-[5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoato de etilo (**D53**) (150mg, 0,38 mmol) se disolvió en etanol (25ml) calentando a 60 °C. La solución se dejó enfriar a TA y después se añadió hidróxido de sodio 2N (3ml, 6
5 mmol). La disolución se agitó a TA durante 30 minutos. LC/MS indicó un solo producto. El etanol se separó por evaporación y el sólido que precipitó en la disolución se separó por filtración. La masa de compuesto del título obtenida como un sólido canera claro al secar fue de 50mg. δ H (400 MHz, d_6 -DMSO) 1,45 (6H, d), 2,67 (2H, t), 4,48 (2H, t), 4,92-4,98 (1H, m), 6,54-6,55 (1H, m), 7,34 (1H, d), 7,38
10 (1H, d), 7,60 (1H, d), 7,91 (1H, dd), 8,35 (1H, d), 8,41-8,46 (2H, m). MS (ES) $C_{23}H_{20}N_4O_4$ requiere 416; encontrado 417 (MH^+).

Ejemplo 21:

3-[4-(5-{3-Ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-
15 il]propanoato de sodio (**E21**)

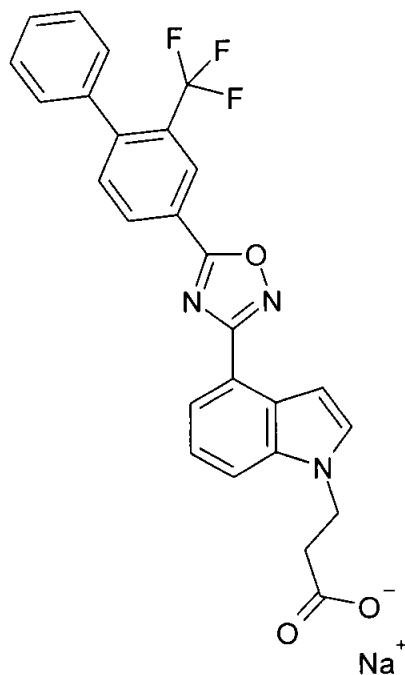
260



3-[4-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoato de etilo (**D63**) (81mg, 0,18 mmol) se disolvió en etanol calentando a 50 °C. Se añadió hidróxido de sodio 2N (0,25ml, 0,5 mmol) seguido de agua (2ml), se calentó a 50 °C para dar una solución clara y después se dejó estar a TA durante 30 minutos. LC/MS indicó un solo producto. El etanol se separó por evaporación para obtener un precipitado que se separó por filtración y se secó. La masa de compuesto del título en forma de sólido marrón pálido obtenida fue 60 mg δ H (400 MHz, d_6 -DMSO) 1,39 (6H, d), 2,32 (2H, t), 4,39 (2H, t), 4,96-5,00 (1H, m), 7,01 (1H, d), 7,31 (1H, t), 7,56-7,61 (2H, m), 7,74 (1H, d), 7,91 (1H, d), 8,45 (1H, dd), 8,55 (1H, d). MS (ES) $C_{23}H_{20}N_4O_4$ requiere 416; encontrado 417 (MH^+).

Ejemplo 22:

3-(4-{5-[2-(Trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de sodio (**E22**)

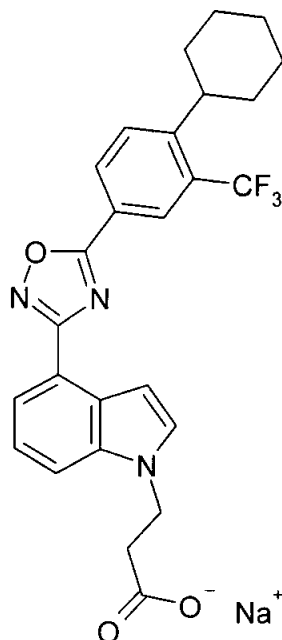


3-(4-{5-[2-(trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-1*H*-indol-1-il)propanoato de
etilo (**D64**) (15mg, 0,31 mmol) se disolvió en etanol (50ml) calentando a 40 °C
durante 10 minutos y después se añadió hidróxido de sodio 2N (4ml, 8 mmol)
5 seguido de agua (8ml). La disolución se dejó estar durante 1 hora. El etanol se
separó por evaporación y se separó por filtración el sólido blanquecino. La masa de
compuesto del título obtenida como un sólido beige al secar fue de 42mg. δ H (400
MHz, metanol- d_4) 2,69 (2H, t), 4,53 (2H, t), 7,17-7,18 (1H, m), 7,32-7,40 (3H, m),
7,46-4,49 (4H, m), 7,66 (1H, d), 7,75 (1H, d), 8,02 (1H, d), 8,53 (1H, dd), 8,63 (1H,
10 d). MS (ES) $C_{26}H_{18}F_3N_3O_3$ requiere 477; encontrado 478 (MH^+).

Ejemplo 23:

3-(4-{5-[4-Ciclohexil-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de sodio (E23)

5

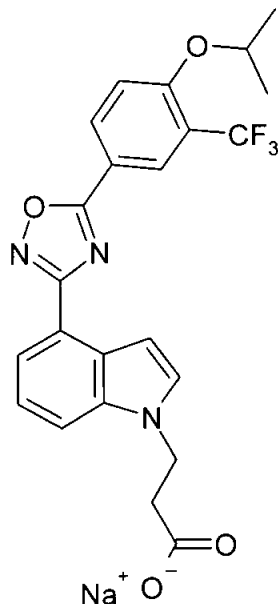


- 3-(4-{5-[4-Ciclohexil-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de etilo (**D69**) (63 mg, 0,123 mmol) se disolvió en etanol (8 ml) y se
- 10 añadió hidróxido de sodio (2M, 0,5 ml, 1,000 mmol). La reacción se calentó a 40 °C durante 18 h. LCMS indicó conversión completa al producto. La mezcla de reacción se concentró *a vacío* y el sólido blanco se separó por filtración y se lavó con agua. Al filtrar, se redisolvió mucho compuesto y pasó al filtrado, así que el sólido y el filtrado se combinaron y separaron entre diclorometano (10 mL) y HCl 2M (3 mL).
- 15 La fase acuosa se extrajo con DCM adicional (10 ml). La fase orgánica se aisló con un separador de fases, se combinó y el disolvente se separó *a vacío*. Después el sólido se disolvió en acetonitrilo y agua con adición de una cantidad equimolar de hidróxido de sodio (2M, 53 µL) antes de que la disolución se liofilizara para dar el compuesto del título (42 mg) en forma de un sólido blanco. δ H (metanol- d_4 , 400 MHz): 8,48 (1H, d), 8,43 (1H, dd), 7,98 (1H, dd), 7,86 (1H, d), 7,73 (1H, d),
- 20 7,46 (1H, d), 7,32 (1H, t aparente), 7,15 (1H, dd), 4,52 (2H, t), 3,04 (1H, t), 2,69 (2H,

t), 2,0-1,8 (5H, m), 1,63 (2H, dd), 1,53-1,37 (3H, m). MS (ES) $C_{26}H_{24}F_3N_3O_3$ requiere 483; encontrado 482 ($M-H^+$).

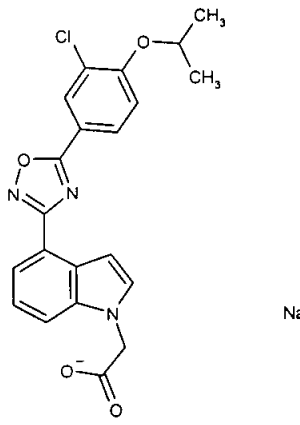
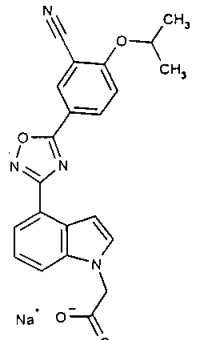
Ejemplo 24:

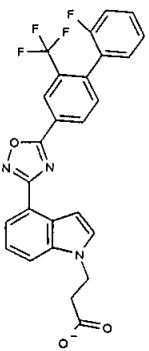
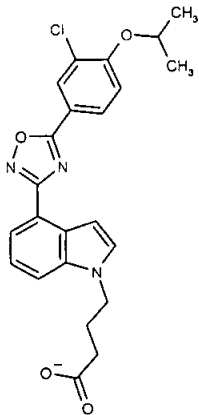
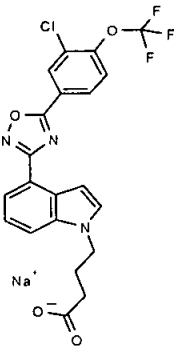
- 5 **3-(4-{5-[4-[(1-Metiletil)oxi]-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il]-1H-indol-1-il)propanoato de sodio (E24)**

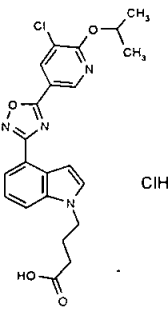
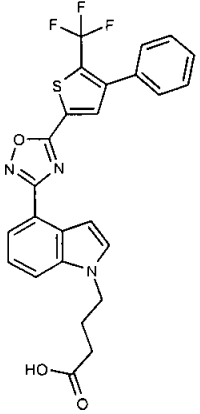
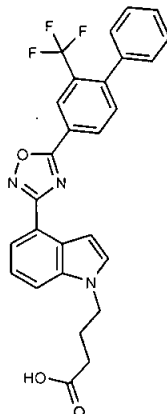


- 10 A una suspensión de 3-(4-{5-[4-[(1-metiletil)oxi]-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il]-1H-indol-1-il)propanoato de etilo (**D72**) (81 mg, 0,17 mmol) en etanol (8mL) se añadió hidróxido de sodio acuoso (2M, 0,8 mL, 1,6 mmol) y la reacción se calentó a 50 °C para disolver los reactivos antes de calentar a 40 °C durante 1 h. El disolvente se separó *a vacío* y el residuo se repartió entre acetato de etilo (20 mL) y agua (20 mL) y se aciduló con ácido clorhídrico acuoso (2M). La fase acuosa se
- 15 extrajo con más acetato de etilo (2 x 20 mL) y los extractos orgánicos combinados se secaron (separador de fases) y concentraron *a vacío*. Después el sólido se disolvió en acetonitrilo y agua con adición de una cantidad equimolar de hidróxido de sodio (2M) antes de que la disolución se liofilizara para dar el compuesto del título (57 mg). δH (d_6 -DMSO, 400 MHz): 8,44 (1H, dd), 8,35 (1H, d), 7,93 (1H, dd), 7,74
- 20 (1H, d), 7,65-7,54 (2H, m), 7,31 (1H, t aparente), 7,00 (1H, dd) 4,99 (1H, septete), 4,38 (2H, t), 2,34 (2H, t), 1,36 (6H, d). MS (ES): $C_{23}H_{20}F_3N_3O_4$ requiere 459; encontrado 460 (MH^+).

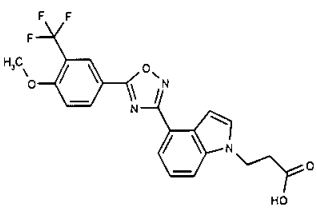
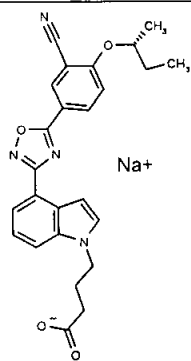
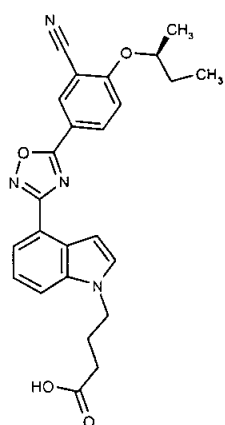
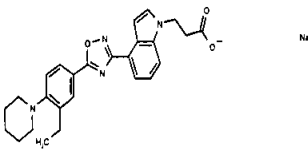
- Los siguientes ejemplos se prepararon por reacciones de hidrólisis similares a las descritas anteriormente. Se usaron al menos dos equivalentes de hidróxido de sodio. El disolvente fue o bien etanol o metanol. En algunos casos se utilizó un codisolvente (diclorometano o dioxano) para facilitar la disolución del material de partida. La reacciones se realizaron a una temperatura entre temperatura ambiente y 50 °C. En algunos casos se separó parte o la totalidad del disolvente cuando la reacción fue completa. La reacciones o bien se trataron repartiéndolas entre una capa orgánica y una capa acuosa o filtrando el producto sólido del disolvente acuoso. En algunos casos los productos brutos se purificaron por trituración. Los productos se aislaron, bien en forma del ácido o de la sal sódica.

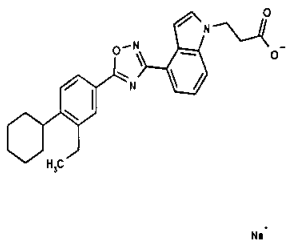
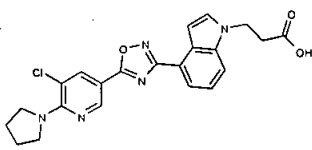
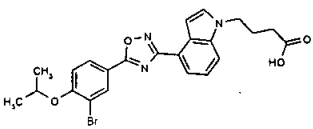
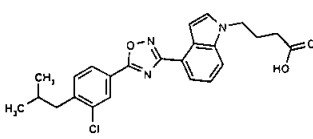
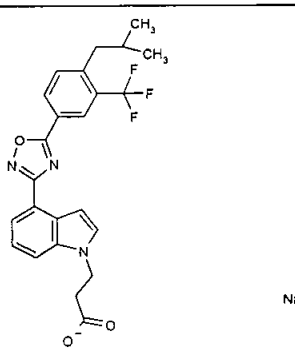
	Estructura	precursor	Nombre	MS
E25		D73	[4-(5-(3-cloro-4-[(1-metiletil)oxi]fenil)-1,2,4-oxadiazol-3-il)-1H-indol-1-il]acetato de sodio	412 (MH ⁺ para ³⁵ Cl)
E26		D74	[4-(5-(3-ciano-4-[(1-metiletil)oxi]fenil)-1,2,4-oxadiazol-3-il)-1H-indol-1-il]acetato de sodio	403 (MH ⁺)

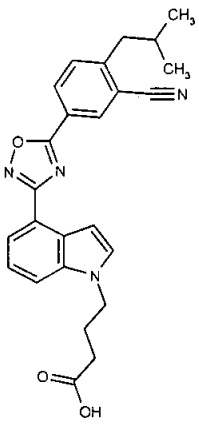
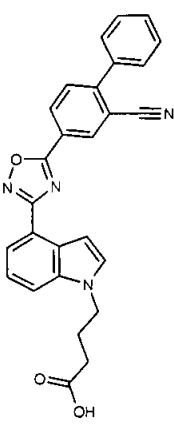
E27	 <chem>[Na+].[O-]C(=O)CCN1Cc2ccccc2c1-c1nc2c(nc12)-c3ccc(cc3C4=CC=CC=C4C(F)(F)F)F</chem>	D76	3-(4-{5-[2'-fluoro-2-(trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de sodio	496 (MH ⁺)
E28	 <chem>[Na+].[O-]C(=O)CCCN1Cc2ccccc2c1-c1nc2c(nc12)-c3ccc(cc3C4=CC=CC=C4C(Cl)=CC(OC(C)C)=C4)Cl</chem>	D77	4-[4-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoato de sodio	440 (MH ⁺ para ³⁵ Cl)
E29	 <chem>[Na+].[O-]C(=O)CCCN1Cc2ccccc2c1-c1nc2c(nc12)-c3ccc(cc3C4=CC=CC=C4C(Cl)=CC(OC(F)(F)F)=C4)Cl</chem>	D78	4-[4-(5-{3-cloro-4-[(trifluorometil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoato de sodio	466 (MH ⁺ para ³⁵ Cl)

E30	 ClH	D79	Hidrocloruro de ácido 4-[4-(5-{5-cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoico	441 (MH ⁺ para ³⁵ Cl)
E31		D80	Ácido 4-(4-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)butanoico	498 (MH ⁺)
E32		D81	Ácido 4-(4-{5-[2-(trifluorometil)-4-biphenilil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)butanoico	492 (MH ⁺)

267

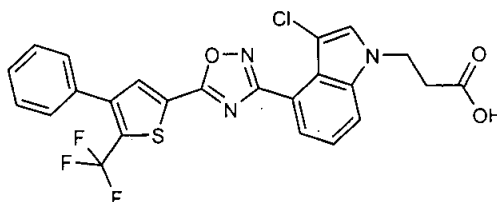
E33		D82	Ácido 3-(4-{5-[4-metiloxi-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico	432 (MH ⁺)
E34		D83	4-{4-[5-(3-ciano-4-{{{(1R)-1-metilpropil}oxi)fenil}-1,2,4-oxadiazol-3-il}-1H-indol-1-il}butanoato de sodio	445 (MH ⁺)
E35		D84	Ácido 4-{4-[5-(3-ciano-4-{{{(1S)-1-metilpropil}oxi)fenil}-1,2,4-oxadiazol-3-il}-1H-indol-1-il}butanoico	445 (MH ⁺)
E36		D85	3-(4-{5-[3-etil-4-(1-piperidinil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de sodio	445 (MH ⁺)

E37	 Na ⁺	D86	3-{4-[5-(4-ciclohexil-3-etilfenil)-1,2,4-oxadiazol-3-il]-1H-indol-1-il}propanoato de sodio	444 (MH ⁺)
E38		D87	Ácido 3-(4-{5-[5-cloro-6-(1-pirrolidinil)-3-piridinil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico	438 (MH ⁺ para ³⁵ Cl)
E39		D88	Ácido 4-[4-(5-{3-bromo-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoico	484 (MH ⁺ para ⁷⁹ Br)
E40		D89	Ácido 4-(4-{5-[3-cloro-4-(2-metilpropil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)butanoico	438 (MH ⁺ para ³⁵ Cl)
E41	 Na ⁺	D90	3-(4-{5-[4-(2-metilpropil)-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de sodio	456 (M-H ⁺)

E42		D91	Ácido 4-(4-{5-[3-ciano-4-(2-metilpropil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)butanoico	429 (MH ⁺)
E43		D92	Ácido 4-(4-{5-(2-ciano-4-bifenilil)-1,2,4-oxadiazol-3-il}-1H-indol-1-il)butanoico	447 (M-H ⁺)

Ejemplo 44:

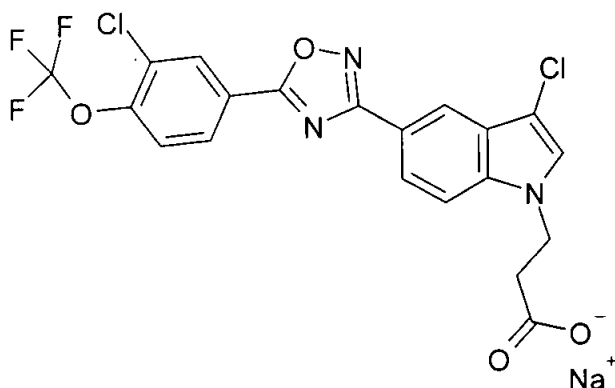
Ácido 3-(3-cloro-4-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico



Este material se preparó de manera similar a **E5** (a partir de **D93**) excepto que la etapa de alquilación llevó 4,5 h en el microondas y la etapa de hidrólisis se llevó a cabo a temperatura ambiente durante una noche. MS (ES): C₂₄H₁₅ClF₃N₃O₃S requiere 517; encontrado 516 (M-H⁺).

Ejemplo 45:

3-[3-cloro-5-(5-{3-cloro-4-[(trifluorometil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoato de sodio(E45)

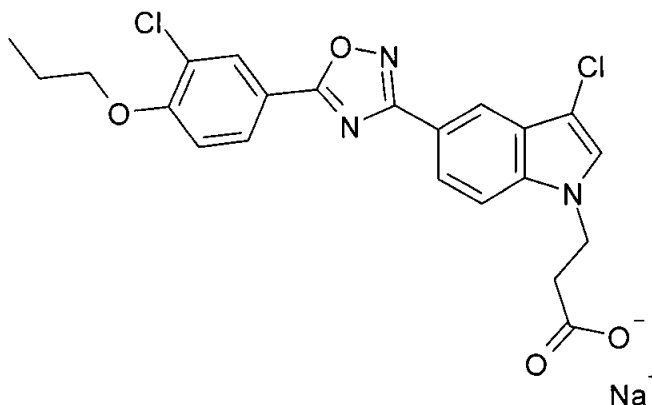


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A 3-[3-cloro-5-(5-{3-cloro-4-[(trifluorometil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoato de etilo (**D97**) (150mg, 2,9 mmol) en etanol (10ml) se añadió NaOH 2N (2ml, 4 mmol) y la mezcla se calentó a 50 °C durante 30 minutos. El etanol se separó por evaporación y el sólido de color crema pálido que había precipitado en la disolución residual se separó por filtración. La masa de compuesto del título
10 obtenida al secar fue de 100mg. δ H (400 MHz, d_6 -DMSO) 2,35 (2H, t), 4,35 (2H, t), 7,73-7,75 (2H, m), 7,86 (1H, d), 7,92 (1H, d), 8,22 (1H, s), 8,30-8,32 (1H, m), 8,49 (1H, d). MS (ES) $C_{20}H_{12}^{35}Cl_2F_3N_3O_4$ requiere 485; encontrado 486 (MH^+)

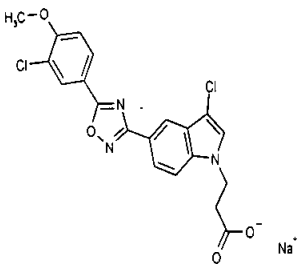
15 **Ejemplo 46:**

3-(3-cloro-5-{5-[3-cloro-4-(propiloxi)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de sodio (E46)

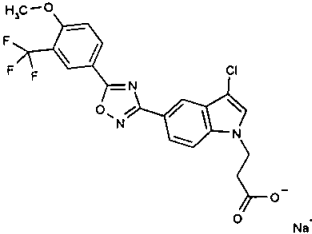
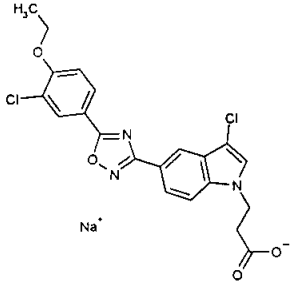
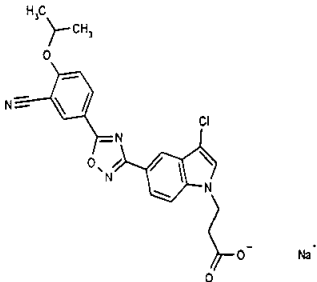


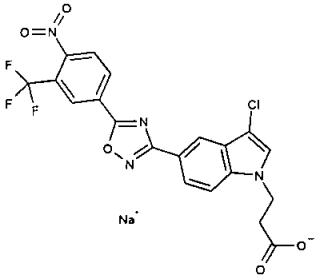
- A 3-(3-cloro-5-{5-[3-cloro-4-(propiloxi)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de etilo (**D101**) (120mg, 2,5 mmol) en etanol (10ml) se añadió NaOH 2N (2ml) y la mezcla se calentó a 50 °C durante 30 minutos. El etanol se separó por evaporación y el sólido de color blanco que había precipitado en la disolución residual se separó por filtración. La masa de compuesto del título obtenida al secar fue de 85mg. δ H (400 MHz, d_6 -DMSO) 1,03 (3H, t), 1,77-1,86 (2H, m), 2,34 (2H, t), 4,17 (2H, t), 4,35 (2H,t), 7,40 (1H,d), 7,71-7,74 (2H,m), 7,91 (1H, d), 8,15 (1H,dd), 8,20-8,21 (2H,m). MS (ES) $C_{22}H_{19}^{35}Cl_2N_3O_4$ requiere 459; encontrado 460 (MH^+).
- 10 Los siguientes ejemplos se prepararon por un método similar a los descritos anteriormente, usando 2-60 equivalentes de hidróxido de sodio (Tabla 8). Las reacciones se trataron eliminando el etanol y filtrando el sólido resultante o extrayendo el producto en acetato de etilo. Si era necesario los productos se purificaban por trituración con éter.

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	Estructura	precursor	Nombre	MS
E47		D102	3-(3-cloro-5-{5-[3-cloro-4-(metiloxi)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de sodio	430, 432 ($M-H^+$ para $^{35}Cl_2$, $^{35}Cl^{37}Cl$)

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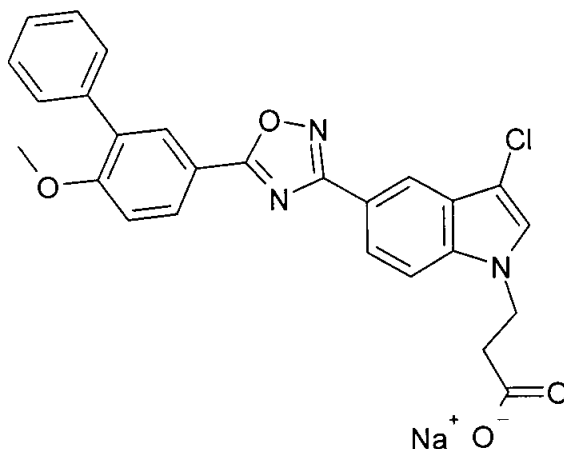
E48		D103	3-(3-cloro-5-{5-[4-(metiloxi)-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de sodio	466 (MH+ para ³⁵ Cl)
E49		D109	3-(3-cloro-5-{5-[3-cloro-4-(etiloxi)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de sodio	444, 446 (M-H ⁺ para ³⁵ Cl ₂ , ³⁵ Cl ³⁷ Cl)
E50		D104	3-[3-cloro-5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoato de sodio	451 (MH+ para ³⁵ Cl)

E51		D105	3-(3-cloro-5-{5-[4-nitro-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de sodio	478, 480 en ES ⁺
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Ejemplo 53:

3-(3-cloro-5-{5-[6-(metiloxi)-3-bifenilil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de sodio (E53)

5

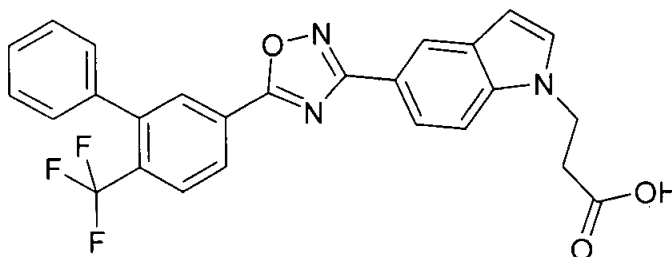


- 3-(3-cloro-5-{5-[6-(metiloxi)-3-bifenilil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoato de etilo (**D107**) (90mg, 0,18 mmol) se calentó en etanol (10ml) para dar una solución clara. Esta disolución se trató con hidróxido de sodio 2N (3ml, 6 mmol) y se agitó a 50 °C durante 30 minutos. El etanol se separó por evaporación y el sólido blanco que precipitó en la disolución se separó por filtración, lavando el sólido con una pequeña cantidad de agua y éter. El sólido se agitó en una pequeña cantidad de acetona durante 1 hora, se filtró, se lavó con una pequeña cantidad de éter y se secó para dar el compuesto del título como 45mg de sólido blanco. δ H (400 MHz, d_6 -DMSO) 2,34 (2H, t), 3,91 (3H, s), 4,34 (2H, t), 7,41-7,46 (2H, m), 7,48-7,50 (2H,

m), 7,57-7,59 (2H, m), 7,63-7,66 (2H, m), 7,80 (1H, d), 8,10 (1H, d), 8,10-8,25 (2H, m). MS (ES) $C_{26}H_{20}^{35}ClN_3O_4$ requiere 473; encontrado 474 (MH^+).

Ejemplo 54

- 5 **Ácido** **3-(5-{5-[6-(trifluorometil)-3-bifenilil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico (E54)**



- Este material se preparó por un método similar para preparar **E53**. El disolvente era una mezcla de etanol y 1,4-dioxano y se usaron 0,071 ml de NaOH ac. 2M para hidrolizar 51 mg de **D113**. MS (ES) $C_{26}H_{18}F_3N_3O_3$ requiere 477; encontrado 476 ($M-H^+$).
- 10

Ensayo de unión a GTP γ S

- 15 Células leucémicas basófilas de rata (RBL) que expresaban establemente el receptor S1P1 se hicieron crecer hasta 80% de confluencia antes de recogerlas en 10ml de solución salina fosfo-tamponada (PBS) y centrifugaron a 1200rpm durante 5 minutos. Después de separar el sobrenadante, el sedimento se resuspendió y homogeneizó en 20 volúmenes de tampón de ensayo (HEPES 20mM pH 7,4, NaCl
- 20 100mM, $MgCl_2 \cdot 6H_2O$ 10mM, GDP 10 μ M Saponina 10 μ g/ml). La suspensión de las membranas se centrifugó adicionalmente durante 20 minutos a 20000rpm, se re-homogeneizó y se hiló de nuevo. Tras la segunda centrifugación, el sedimento se resuspendió en un volumen apropiado (1ml para cada matraz de células) y se analizó para determinar la concentración de proteínas.

25

- La disolución madre concentrada de S1P se sonicó antes de preparar diluciones seriadas a partir de una concentración inicial de 10^{-5} M. Las membranas diluidas (10 μ g/podichlo) se incubaron con varias concentraciones de S1P y 0,3nM ^{35}S -GTP γ S (NEN; actividad específica 1250 Ci/mmol) en placas de 96 pocillos profundos. La
- 30 unión se hizo a 30°C durante 45 minutos y se terminó recogiendo las membranas sobre placas filtrantes GF/B usando un Colector Universal Packard. Después de

775

- secar las placas durante 45 minutos, se añadieron 50µl de Microscint 0 a cada pocillo y se midió la unión en un A pcount NXT (Perkin Elmer). Los datos se analizaron utilizando Graphpad Prism 4 y se expresaron como estimulación porcentual respecto del valor basal. Los valores EC50 se definieron como la
- 5 concentración de agonista requerida para dar 50% de la estimulación máxima.

Ensayo GTP γ S (método alternativo)

- Se homogeneizaron membranas S1P1 de células de hepatoma de rata (RH-7777) que expresan S1P1 haciéndolas pasar a través de una aguja 23G needle y después
- 10 se aplicó un pulso de 3 segundos usando un homogeneizador Ultra Turrax. Las membranas se diluyeron a la concentración requerida (1,5µg/pocillo) y se adhirieron a perlas de ensayo de proximidad por centelleo revestidas con Aglutinina de germ de trigo (0,125mg/pocillo) en tampón de ensayo (HEPES 20mM, MgCl₂ 10mM, NaCl 100mM y el pH se ajustó a 7,4 usando KOH 5M), GDP 10µM FAC y también se
- 15 añadió saponina 90µg/ml FAC).

- Después de 30 minutos de pre-acoplamiento sobre hielo, la suspensión de perlas y membranas se dispensó en una placa de pocillos LV384 de polipropileno Greiner blancos (5µl/pocillo), que contenía 0,1µl del compuesto. Después se añadieron a las placas de agonista 5µl de [³⁵S]-GTP γ S /pocillo (concentración final de radioligandos
- 20 0,5nM) preparada en tampón de ensayo. La disolución final de ensayo (10,1µl) se leyó entonces inmediatamente en un lector Viewlux.

Los datos se analizaron usando una ecuación logística de cuatro parámetros puntuales que usaba el paquete de software XC50.

- 25 Los compuestos ejemplificados de la invención que se ensayaron en este análisis tenían un pEC50 > 5.

S1P3

- Se homogeneizaron membranas S1P3 de células leucémicas basófilas de rata (RBL-2H3) que expresan S1P3 haciéndolas pasar a través de una aguja 23G needle y después se aplicó un pulso de 3 segundos usando un homogeneizador Ultra Turrax. Las membranas se diluyeron a la concentración requerida (1,5µg/pocillo) y se adhirieron a perlas de ensayo de proximidad por centelleo revestidas con Aglutinina de germ de trigo (0,125mg/pocillo) en tampón de ensayo (HEPES 20mM,
- 30

MgCl₂ 10mM, NaCl 100mM y el pH se ajustó a 7,4 usando KOH 5M); GDP 10 μ M FAC y también se añadió saponina 90 μ g/ml FAC).

Después de 30 minutos de pre-acoplamiento sobre hielo, la suspensión de perlas y membranas se dispuso en una placa de pocillos LV384 de polipropileno Greiner blancos (5 μ l/pocillo), que contenía 0,1 μ l del compuesto. Después se añadieron a las placas de agonista 5 μ l de [³⁵S]-GTP γ S /pocillo (concentración final de radioligandos 0,3nM) preparada en tampón de ensayo. La disolución final de ensayo (10,1 μ l) se leyó entonces inmediatamente en un lector Viewlux.

Los datos se analizaron usando una ecuación logística de cuatro parámetros puntuales que usaba el paquete de software XC50.

Los compuestos ejemplificados ensayados en este análisis tenían un pEC₅₀ < 6, y muchos tenían un pEC₅₀ <5.

15

Ensayo en levadura

Se generaron células de levadura (*Saccharomyces cerevisiae*) que expresan el receptor S1P1 humano por integración de una cassette de expresión en el locus cromosómico *ura3* de la cepa de levaduras MMY23. Este casete consistía en una secuencia de ADN que codificaba el receptor S1P1 humano flanqueada por el promotor de levadura GPD hacia el extremo 5' de S1P1 y una secuencia terminadora de la transcripción de levadura hacia el extremo 3' de S1P1. La cepa MMY23 expresa una subunidad alfa de la proteína G quimérica de levaduras/mamíferos en la que los 5 aminoácidos C-terminales de Gpa1 están reemplazados por los 5 α 2 aminoácidos C-terminales de Gi1/2 humana (como se describe en Brown *et al.* (2000), *Yeast* **16**:11-22). Las células se cultivaron a 30°C en medio de levaduras Synthetic Complete (SC) líquido (Guthrie y Fink (1991), *Métodos en Enzymology*, Vol. 194) que carecía de uracilo, triptófano, adenina y leucina hasta una fase logarítmica tardía (aproximadamente 6 DO₆₀₀/ml).

Los agonistas se prepararon como soluciones madre 10 mM en DMSO. Los valores de CE₅₀ (la concentración requerida para producir 50% de la respuesta máxima) se calcularon usando diluciones 4x (BiomekFX, Beckman) en DMSO. Las soluciones de agonista en DMSO (volumen de ensayo final 1%) se transfirieron a placas de microtitulación de fondo negro transparente de Greiner (384 pocillos). Las células se suspendieron a una densidad de 0,2 DO₆₀₀/ml en medio SC que carecía de histidina, uracilo, triptófano, adenina y leucina y se suplementaron con 3-aminotriazol 0,1 mM,

fosfato sódico 0,1M, pH 7,0, y fluoresceína di-β-D-glucopiranosido (FDGlu) 10 M. Esta mezcla (50 μl por pocillo) se añadió al agonista en las placas de ensayo (Multidrop 384, Labsystems). Después de la incubación a 30°C durante 24 horas, se determinó la fluorescencia resultante de la degradación de FDGlu a fluoresceína debido a la exoglucanasa, una enzima de levaduras endógena producida durante el crecimiento celular estimulado por agonistas, se determinó usando un lector de placas de microtitulación de fluorescencia (Tecan Spectrofluor o LJI Analyst longitud de onda de excitación: 485 nm; longitud de onda de emisión: 535 nm). Se representó la fluorescencia frente a la concentración de compuesto y se ajustó la curva iterativamente usando un ajuste de cuatro parámetros para generar un valor de efecto frente a concentración. La eficacia (E_{max}) se calculó a partir de la ecuación

$$E_{max} = \frac{Max_{[compuesto X]} - Min_{[compuesto X]}}{Max_{[S1P]} - Min_{[S1P]}} \times 100\%$$

donde $Max_{[compuesto X]}$ y $Min_{[compuesto X]}$ son el máximo y mínimo ajustado respectivamente a partir de la curva de concentración frente al efecto para el compuesto X, y $Max_{[S1P]}$ y $Min_{[S1P]}$ son el máximo y el mínimo ajustados respectivamente a partir de la curva de concentración frente al efecto para 1-fosfato de esfingosina (obtenible a partir de Sigma). Los valores de la relación molar equieficaz (EMR) se calcularon a partir de la ecuación

$$EMR = CE_{50 [compuesto X]} / CE_{50 [S1P]}$$

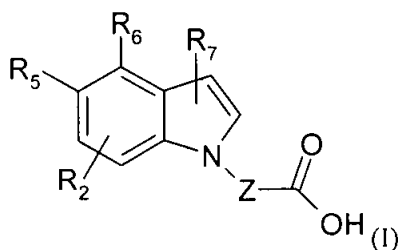
donde $CE_{50 [compuesto X]}$ es la CE_{50} del compuesto X y $CE_{50 [S1P]}$ es la CE_{50} de S1P.

Cuando se ensayaron, los compuestos ejemplificados de la invención tenían un $pEC_{50} > 4,5$ en el ensayo de levaduras.

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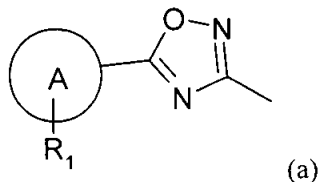
REIVINDICACIONES

- 5 1. Un compuesto de fórmula (I) o una de sus sales farmacéuticamente aceptables:



en la que

- 10 uno de R_5 y R_6 es hidrógeno o R_2 y el otro es (a)



A es un fenilo o un anillo heteroarílico de 5 o 6 miembros;

- R_1 es hidrógeno o hasta tres sustituyentes independientemente seleccionados de
- 15 halógeno, alquilo $C_{(1-6)}$, cicloalquilo $C_{(3-6)}$, alcoxi $C_{(1-6)}$, cicloalquilo $C_{(3-6)}$, trifluorometoxi, difluorometoxi, trifluorometilo, ciano, nitro, piperidina opcionalmente sustituida, pirrolidina opcionalmente sustituida, fenilo opcionalmente sustituido y anillos heteroarílicos de 5 ó 6 miembros opcionalmente sustituidos;
- cuando R_1 es fenilo, piperidina, pirrolidina o un anillo heteroarílico de 5 ó 6 miembros
- 20 puede estar sustituido con hasta tres sustituyentes seleccionados de halógeno, alquilo $C_{(1-6)}$, alcoxi $C_{(1-6)}$, trifluorometoxi, difluorometoxi, cicloalquilo C_{3-6} , trifluorometilo y ciano;

- R_2 es hidrógeno o hasta tres sustituyentes independientemente seleccionados de
- halógeno, alquilo $C_{(1-4)}$, alcoxi $C_{(1-4)}$, trifluorometoxi, difluorometoxi, trifluorometilo y
- 25 ciano;

R_7 es hidrógeno o halógeno;

Z es alquilo $C_{(1-4)}$ que está opcionalmente interrumpido con N o O y está opcionalmente sustituido con halógeno o metil.

ZAA

2. Un compuesto de fórmula (I) o una de sus sales farmacéuticamente
5 aceptables, donde:

R₅ es hidrógeno y R₆ es (a); y/o

A es tienilo, piridilo o fenilo; y/o

- R₁ es hasta tres sustituyentes seleccionados de halógeno, alcoxi C₁₋₆, o
trifluorometilo, fenilo opcionalmente sustituido, ciclohexilo opcionalmente sustituido,
10 ciano, trifluorometoxi, piperidina opcionalmente sustituida, pirrolidina opcionalmente
sustituida, alquilo C₁₋₆ y NO₂; y/o

R₂ es hidrógeno; y/o

R₇ es hidrógeno o halógeno; y/o

- Z es alquilo C₍₁₋₄₎ que está opcionalmente interrumpido con N o O y está
15 opcionalmente sustituido con fluoro o metilo.

3. Un compuesto seleccionado de:

- Ácido 3-(5-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1*H*-indol-1-
20 il)propanoico

Ácido 3-[5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1*H*-indol-1-
il]propanoico

- 25 Ácido 3-[3-cloro-5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1*H*-indol-1-
il]propanoico

- Ácido 3-(3-cloro-5-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1*H*-indol-
1-il)propanoico

30

Ácido 3-(4-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1*H*-indol-1-
il)propanoico

- 35 Ácido 3-[4-(5-{3-cloro-4-[(trifluorometil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1*H*-indol-1-
il]propanoico

- Ácido 3-[4-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoico
- 5 Ácido 3-[4-(5-{5-cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoico
- Ácido 3-[5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoico
- 10 Ácido (5-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)acético
- Ácido 3-[3-bromo-5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoico
- 15 Ácido 5-[5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]pentanoico
- Ácido 4-[5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoico
- 20 Ácido 4-[5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoico
- Ácido (2S)-3-[5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]-2-metilpropanoico
- 25 2-metilpropanoico
- Ácido 2,2-dimetil-3-(5-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- 30 Ácido 3-[5-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]-2,2,3-trifluoropropanoico
- Ácido 4-[4-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoico
- 35

- Ácido 3-[5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoico
- 5 Ácido 3-[4-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoico
- Ácido 3-(4-{5-[2-(trifluorometil)-4-biphenilil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- 10 Ácido 3-(4-{5-[4-ciclohexil-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- Ácido 3-(4-{5-[4-[(1-metiletil)oxi]-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- 15 Ácido [4-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]acético
- Ácido [4-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]acético
- 20 Ácido 3-(4-{5-[2'-fluoro-2-(trifluorometil)-4-bifenilil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- Ácido 4-[4-(5-{3-cloro-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoico
- 25 Ácido 4-[4-(5-{3-cloro-4-[(trifluorometil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoico
- Ácido 4-[4-(5-{5-cloro-6-[(1-metiletil)oxi]-3-piridinil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]butanoico
- 30 Ácido 4-(4-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)butanoico
- 35 Ácido 4-(4-{5-[2-(trifluorometil)-4-biphenilil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)butanoico

- Ácido 3-(4-{5-[4-metiloxi-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- 5 Ácido 4-{4-[5-(3-ciano-4-{[(1R)-1-metilpropil]oxi}fenil)-1,2,4-oxadiazol-3-il]-1H-indol-1-il}butanoico
- Ácido 4-{4-[5-(3-ciano-4-{[(1S)-1-metilpropil]oxi}fenil)-1,2,4-oxadiazol-3-il]-1H-indol-1-il}butanoico
- 10 Ácido 3-(4-{5-[3-etil-4-(1-piperidinil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- Ácido 3-{4-[5-(4-ciclohexil-3-etilfenil)-1,2,4-oxadiazol-3-il]-1H-indol-1-il}propanoico
- 15 Ácido 3-(4-{5-[5-cloro-6-(1-pirrolidinil)-3-piridinil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- Ácido 4-[4-{5-[3-bromo-4-{(1-metiletil)oxi}fenil]-1,2,4-oxadiazol-3-il]-1H-indol-1-il}butanoico
- 20 Ácido 4-(4-{5-[3-cloro-4-(2-metilpropil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)butanoico
- 25 Ácido 3-(4-{5-[4-(2-metilpropil)-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il]-1H-indol-1-il)propanoico
- Ácido 4-(4-{5-[3-ciano-4-(2-metilpropil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)butanoico
- 30 Ácido 4-{4-[5-(2-ciano-4-bifenilil)-1,2,4-oxadiazol-3-il]-1H-indol-1-il}butanoico
- Ácido 3-(3-cloro-4-{5-[4-fenil-5-(trifluorometil)-2-tienil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico
- 35

Ácido 3-[3-cloro-5-(5-{3-cloro-4-[(trifluorometil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoico

5 Ácido 3-(3-cloro-5-{5-[3-cloro-4-(propiloxi)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico

Ácido 3-(3-cloro-5-{5-[3-cloro-4-(metiloxi)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico

10 Ácido 3-(3-cloro-5-{5-[4-(metiloxi)-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico

15 Ácido 3-(3-cloro-5-{5-[3-cloro-4-(etiloxi)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico

Ácido 3-[3-cloro-5-(5-{3-ciano-4-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoico

20 Ácido 3-(3-cloro-5-{5-[4-nitro-3-(trifluorometil)fenil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico

Ácido 3-[3-cloro-5-(5-{4-cloro-3-[(1-metiletil)oxi]fenil}-1,2,4-oxadiazol-3-il)-1H-indol-1-il]propanoico

25 Ácido 3-(3-cloro-5-{5-[6-(metiloxi)-3-bifenilil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico

3-(5-{5-[6-(trifluorometil)-3-bifenilil]-1,2,4-oxadiazol-3-il}-1H-indol-1-il)propanoico

30 y sus sales farmacéuticamente aceptables.

4. Uso de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 3 para el tratamiento de afecciones o trastornos mediados por receptores S1P1.

35 5. Uso según la reivindicación 4, donde la afección o el trastorno es esclerosis múltiple, enfermedades autoinmunitarias, trastornos inflamatorios crónicos, asma,

neuropatías inflamatorias, artritis, trasplantes, enfermedad de Crohn, colitis ulcerosa, lupus eritematoso, psoriasis, lesión por isquemia-reperfusión, tumores sólidos, y metástasis tumoral, enfermedades asociadas con angiogénesis, enfermedades vasculares, estados dolorosos, enfermedades víricas agudas, estados inflamatorios
5 intestinales, diabetes insulín y no-insulín-dependientes.

6. Uso según la reivindicación 4, donde la afección es esclerosis múltiple.

7. Uso de un compuesto de acuerdo con una cualquiera de las reivindicaciones
10 1 a 3 para fabricar un medicamento para su uso en el tratamiento de afecciones o trastornos mediados por receptores S1P1.

8. Uso según la reivindicación 4, donde la afección o el trastorno es esclerosis múltiple, enfermedades autoinmunitarias, trastornos inflamatorios crónicos, asma,
15 neuropatías inflamatorias, artritis, trasplantes, enfermedad de Crohn, colitis ulcerosa, lupus eritematoso, psoriasis, lesión por isquemia-reperfusión, tumores sólidos, y metástasis tumoral, enfermedades asociadas con angiogénesis, enfermedades vasculares, estados dolorosos, enfermedades víricas agudas, estados inflamatorios intestinales, diabetes insulín y no-insulín-dependientes.

20

9. Uso según la reivindicación 7, donde la afección es esclerosis múltiple.

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

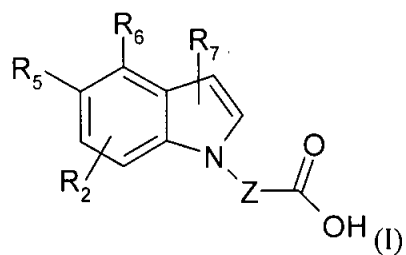
25

11. Un método de tratamiento de afecciones o trastornos en mamíferos incluyendo los seres humanos que pueden estar mediados por los receptores S1P1.

12. Un método de tratamiento según la reivindicación 11, en donde la afección
30 es esclerosis múltiple.

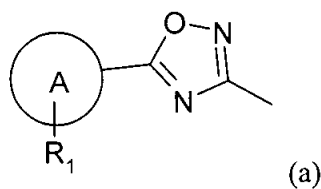
Resumen

La invención se refiere a compuestos de fórmula (I)



en la que

uno de R_5 y R_6 es hidrógeno o R_2 y el otro es (a)



5

procedimientos para su preparación, composiciones farmacéuticas que los contienen y su uso en el tratamiento de afecciones o trastornos que están mediados por el receptor S1P1.

10

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference JEG/PB62261	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, Item 5 below.	
International application No. PCT/EP2007/064185	International filing date (day/month/year) 19/12/2007	(Earliest) Priority Date (day/month/year) 21/12/2006
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 5 sheets.

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

1. Basis of the report

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

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

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

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

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

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

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

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

INDOLE DERIVATIVES AS 51P1 RECEPTOR AGONISTS

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

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

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

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/064185

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/04 C07D413/14 A61K31/405 A61P37/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 2007/116866 A (ASTELLAS PHARMA INC [JP]; HARADA HIRONORI [JP]; HATTORI KAZUYUKI [JP];) 18 October 2007 (2007-10-18) cited in the application page 49; compounds 47-4, 47-9, 47-10, 47-12	1-12
P, A	JP 2007 262009 A (DAIICHI SEIYAKU CO) 11 October 2007 (2007-10-11) the whole document	1-12
A	WO 2004/103279 A (MERCK & CO INC [US]; COLANDREA VINCENT J [US]; DOHERTY GEORGE A [US];) 2 December 2004 (2004-12-02) page 5, line 15 - page 8, line 9 page 39, line 1 - page 39, line 10 ----- -/--	1-12

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

☒ See patent family annex.

* Special categories of cited documents:

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

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

18 April 2008

Date of mailing of the international search report

25/04/2008

Name and mailing address of the ISA/

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

Authorized officer

Usueli, Ambrogio

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/064185

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/032465 A (MERCK & CO INC [US]; DOHERTY GEORGE A [US]; HALE JEFFREY J [US]; LEGIE) 14 April 2005 (2005-04-14) page 5, line 11 - page 6, line 24 page 13, line 30 - page 14, line 6 -----	1-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/064185**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

Although claims 4-6, 11, 12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2007/064185

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2007116866	A	18-10-2007	NONE	
JP 2007262009	A	11-10-2007	NONE	
WO 2004103279	A	02-12-2004	AU 2004240586 A1	02-12-2004
			CA 2524867 A1	02-12-2004
			CN 1788008 A	14-06-2006
			EP 1625123 A2	15-02-2006
			JP 2006528980 T	28-12-2006
WO 2005032465	A	14-04-2005	AU 2004277947 A1	14-04-2005
			CA 2539438 A1	14-04-2005
			CN 1859908 A	08-11-2006
			EP 1670463 A2	21-06-2006
			JP 2007528872 T	18-10-2007
			US 2007043014 A1	22-02-2007

PATENT COOPERATION TREATY

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From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

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

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

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

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2007/064185

International filing date (day/month/year)
19.12.2007

Priority date (day/month/year)
21.12.2006

International Patent Classification (IPC) or both national classification and IPC
INV. C07D413/04 C07D413/14 A61K31/405 A61P37/00

Applicant
GLAXO GROUP LIMITED

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

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

2. **FURTHER ACTION**

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

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

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

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

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Usuelli, Ambrogio

Telephone No. +49 89 2399-7366



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2007/064185

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:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/EP2007/064185**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

- ☐ the entire international application
- ☒ claims Nos. 4-6,11,12 (patentability)

because:

- ☒ the said international application, or the said claims Nos. 4-6,11,12 (patentability) relate to the following subject matter which does not require an international search (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See Supplemental Box for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2007/064185

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

1. Statement

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

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2007/064185

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 4-6, 11 and 12 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1 (iv)/67.1(iv) PCT.

Re Item V

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

1- Reference is made to the following documents:

- d3: WO 2004/103279 A (MERCK & CO INC [US]; COLANDREA VINCENT J [US]; DOHERTY GEORGE A [US];) 2 December 2004 (2004-12-02)
- d4: WO 2005/032465 A (MERCK & CO INC [US]; DOHERTY GEORGE A [US]; HALE JEFFREY J [US]; LEGIE) 14 April 2005 (2005-04-14)

2- Novelty

Present compounds differ from the compounds disclosed in d3 and d4 mainly on account of the indole ring.

The requirements of Art. 33.2 PCT are therefore met.

3- Inventive Step

3.1- Starting from d4 which is regarded as the closest state of the art, the technical problem underlying the invention can be seen in the provision of further agonists of the S1P1 sphingosine receptor.

The experimental results disclosed on pages 122, 123 of the application indicate that present compounds of formula (I) indeed solve the problem defined above.

3.2- Neither d3 nor d4 disclose S1P1 agonists containing an indole linked through a chain to a carboxy moiety.

In view of this structural feature, present compounds are considered inventive.

Re Item VI

Certain documents cited

296.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2007/064185

d1: WO 2007/116866 A (ASTELLAS PHARMA INC [JP]; HARADA HIRONORI [JP];
HATTORI KAZUYUKI [JP];) 18 October 2007 (2007-10-18) cited in the application

d2: JP 2007 262009 A (DAIICHI SEIYAKU CO) 11 October 2007 (2007-10-11)

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 297

020

Bogotá D.C.,

Dotor(a)

LARTE GARCIA CARLOS REYNALDO

poderado(a) y/o Representante de

LAXO GROUP LIMITED

REFERENCIA

Radicación No.	9 62875
Solicitud internacional	PCT/EP2007/064185
Fecha inicio fase nacional	21/07/2009
Trámite	11
Evento	378
Actuación	416
Oficio No.	8547
Folios	1

Enviando en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Úmplase

ado en Bogotá DC,

13 JUL. 2009

LIX CARMENZA CESPEDES DE VERGEL

efe de la división de Nuevas Creaciones

dpall