



Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

06-98507

21. EXPEDIENTE No.

54. TÍTULO 1,3,4-Oxadiazol-2-onas como moduladores del PPAR delta y los usos de las mismas.

51. CLASIFICACIÓN INTERNACIONAL C07D 271/00 ; A61K 31/4.

71. SOLICITANTE Aventis Pharmaceuticals Inc.

DOMICILIO

74. APODERADO Bridgewater, New Jersey, Estados Unidos

22. BOGOTÁ, D. C., 29 de Septiembre de 2006

S.S.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-098507- -00000-0000
Fee: 2006-09-29 16:23:36 Dep. 2020 MUECREACIONES
Trz. 11 PATENTE/IN
Eve: 376 FABENACIONALI
Act 411 PRESENTACION. Folios 135

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

01-Nov-06

①

SOLICITUD DE :



Patente de Invención.



Patente de Modelo de Utilidad.



Capítulo I.



Capítulo II.

②

SOLICITANTE
(71)

Nombre: AVENTIS PHARMACEUTICALS INC.

Dirección: 300 Somerset Corporate Boulevard,
Bridgewater, NJ 08807-2854 Estados Unidos

Nacionalidad o Domicilio: Bridgewater, New Jersey,
Estados Unidos

Lugar de Constitución: Estados Unidos

Teléfono:

Fax:

IDENTIFICACION

C.C. ☐

NIT ☐

C.E. ☐

Otro ☐

Cual

Número

REPRESENTANTE
O APODERADO

Nombre: LUIS PATIÑO LEYVA

Dirección Cra. 11ª No. 94-76 - Of. 308

Teléfono: 6161948

Fax: 6163976

E-mail:

IDENTIFICACION

C.C. ☒

NIT ☐

C.E. ☐

Otro ☒

Cual

Número 2.930.616 TP 2698

④

INVENTOR (ES)
(72)

Nombre: MCGARRY Daniel G.

Dirección: 205 Carol Jean Way,

Nacionalidad o Domicilio: Branchburg, NJ 08876, Estados Unidos

PCT (86)

Solicitud Internacional No. PCT/US2005/010854

Fecha Marzo 30 de 2005

WO 2005/097762 A2

Publicación Internacional No. WO 2005/097762 A3

Fecha Octubre 20 de 2005

⑥ Título (54) 1,3,4-OXADIAZOL-2-ONAS COMO MODULADORES DEL PPAR DELTA Y LOS USOS DE LAS MISMAS.

⑦

Clasificación Internacional (51) C07D 271/00

2 AGI LX 31/12/05

⑧

PRIORIDAD:

(33) País de Origen

(32) Fecha

(31) Numero de Solicitud

SI ☒ NO ☐

Estados Unidos

Abril 1 de 2004

60/558,419

⑨

Comprobante de pago: 06-74,958

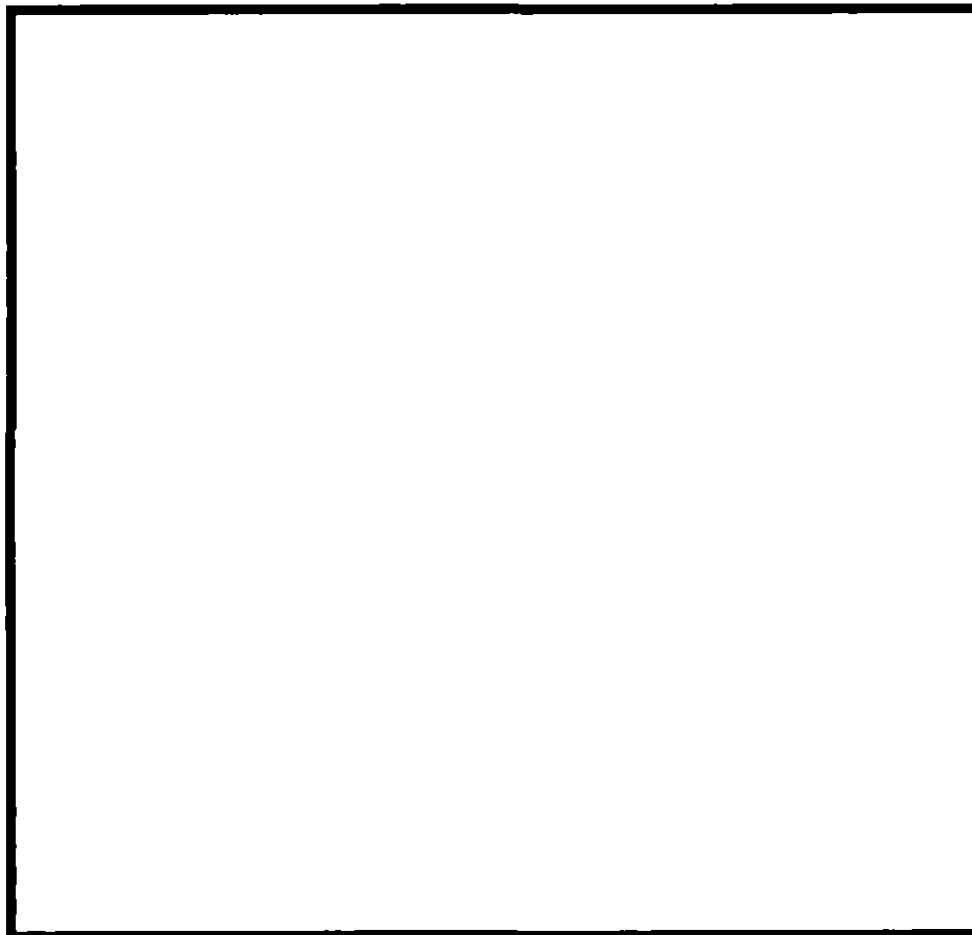
Fecha: Septiembre 27 de 2006

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

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredite existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☒ 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 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros Reporte de Búsqueda Internacional.

(11) FIGURA CARACTERISTICA



(12) Solicito la concesión de la patente,

NOMBRE: LUIS PATIÑO LEYVA

FIRMA: 

C.C. 2.930.616 Bogotá T.P. 2698

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

Continuación nombre, dirección y domicilio de inventores:

<u>Nombre</u>	<u>Dirección</u>	<u>Domicilio</u>
CHANDROSS Karen	13 Staudt Court,	Sommerset, NJ08873 Estados Unidos
MERRILL Jean	101 Alpine Lane,	Whippany, Nwe Jersey 07981 Estados Unidos
GOERLITZER Jochen	Stegstrasse 60,	D-60954 Frankfurt am Main, Alemania
KEIL Stefanie	Am Kreishaus 12,	65719 Hofheim, Alemania
WENDLER Wolfgang	Haintchener Str. 12ª,	65618 Selters, Alemania
BERNARDELLI Patrick	14 rue Auguste Rodin,	F-78450 Villepreux, Francia

Otros anexos que se acompañan a la solicitud.

Formulario No. PCT/RO/101 correspondiente a la solicitud de patente internacional, con su traducción al castellano.

Formulario PCT/IB/304 concerniente a la transmisión del documento de prioridad.

Formulario PCT/IB/306 referente a la notificación de un cambio.

Formulario PCT/ISA/210 referente a Reporte de Búsqueda Internacional.

Formulario PCT/ISA/237 correspondiente a la opinión escrita de la Búsqueda Internacional autorizada.

Formulario PCT/IB/308 informando al solicitante de una comunicación de la solicitud internacional a las oficinas designadas.

Formulario PCT/IB/308 correspondiente a la segunda y suplementaria noticia informando al solicitante de la comunicación de la solicitud internacional a las oficinas designadas

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-088507- -00000-0000
Fec: 2006-09-29 16:23:36 Dep. 2020 NUECREACIONES
Trib. 11 PATENTEYII
Evo: 376 FASENACIONALI
Act411 PRESENTACION Folio: 135

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 74,950
FECHA : SEPTIEMBRE 27 DE 2006

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
MANUEL MIRANDA	CONSIGNACION	BANCO POPULAR	050-00110-6	53371884	27/09/2006	2,315,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	463,000.00
		TOTAL :	463,000.00

CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE :  09.21.58844

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

7 5 +

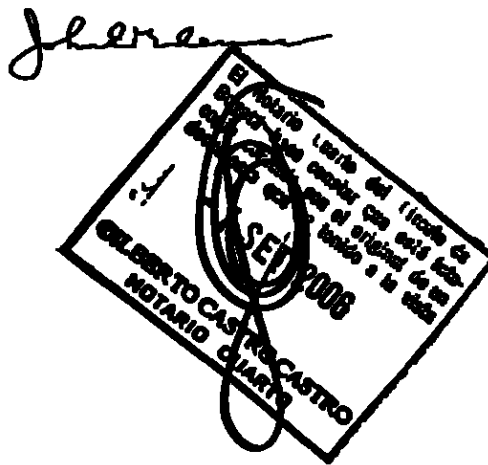
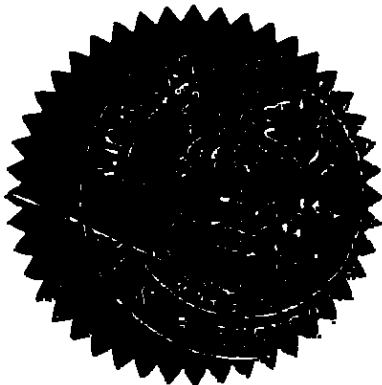
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
R. PETER WIDIN
3. ACTING IN THE CAPACITY OF:
COUNTY CLERK
4. BEARS THE SEAL/STAMP OF:
COUNTY OF SOMERSET

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 9TH DAY OF APRIL 2002
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER
8. NO. A149012
9. SEAL/STAMP:
10. SIGNATURE



G. HOLLMANN RESTREPO
ABOGADOS LTDAG. HOLLMANN RESTREPO
ABOGADOS LTDA

The undersigned, acting on behalf of and representing of AVENTIS PHARMACEUTICALS INC, domiciled in 300 Somerset Corporate Boulevard, Bridgewater, New Jersey, USA, hereby appoint(s) GUSTAVO HOLLMANN RESTREPO and/or LUIS PATIÑO LEYVA, domiciled in Bogotá D.C., Republic of Colombia, as our true and legal attorney with the necessary powers:

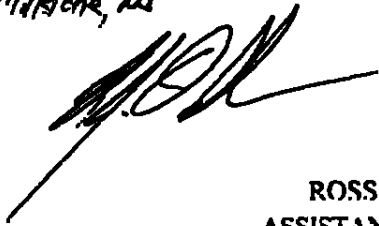
1) To apply to the administrative, judicial and police authorities of the Republic of Colombia, in any instance or appeal, for obtaining registration of patents, utility models, industrial designs and models, commercial engravings and names, trademarks, slogans, health licenses, copyrights and domain names as well as their assignments, extensions, renewals and changes of name; 2) To prepare, apply for, obtain, execute and register contracts, licenses, authorizations and registrations of any kind; 3) To intervene as plaintiff or defendant, in any instance or appeal, before any judge, court, tribunal, corporation, public officer or authority in any judicial, administrative or police action, such as: action dealing with commercial engravings and names; oppositions against trademark registrations; caducity and nullity actions; recovery actions, actions arising from obtainment and working of license agreements; actions dealing with unfair competition; criminal actions; actions claiming indemnity for damages, complaints or remarks on all sort of industrial property matters; the performance of precautionary measures, and in any other similar action, measure or appeal related to intellectual property matters.

To this effect, I (we) hereby authorize him to file applications, make descriptions, protests, amendments, declarations, oppositions, cancellations, appeals and claims; to pay taxes, quotas and liens as provided by Law; to waive or abandon granted rights or rights in process of being granted, to receive all kind of documents and securities; to issue the respective releases and, in general, to take, before said authorities, pertinent steps to the above mentioned purposes and take all measures they may deem advisable to protect my (our) interests, with all other necessary legal faculties, and I (we) hereby declare as good and valid whatever the attorneys should do to my (our) benefit.

This power comprises the authority to ratify or confirm on my (our) behalf any action, as well as the faculty of receiving, desisting, transacting, compromising, substituting and revoking substitutions, taking modifications, and appointing judicial or extra-judicial attorneys.

Signed in on this 1st day of March of 2002.

East Millstone, NJ



ROSS J. OEHLER
ASSISTANT SECRETARY

Yo (nosotros), obrando en nombre propio y representación de AVENTIS PHARMACEUTICALS INC, con domicilio en 300 Somerset Corporate Boulevard, Bridgewater, New Jersey, Estados Unidos de América, nombro(amos) a GUSTAVO HOLLMANN RESTREPO y/o LUIS PATIÑO LEYVA, con domicilio en Bogotá D.C., República de Colombia, Ora 11^a No 94-76, Oficina 308, apoderado verdadero y legal, con poder especial, amplio y suficiente:

1) Para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía en cualquier instancia o recurso, la obtención de patentes de invención, modelos de utilidad, dibujos y modelos industriales, registro de marcas, registro de lemas comerciales, depósito de nombres y enseñanzas comerciales, registros sanitarios, derechos de autor y nombres de dominio así como sus traspasos, prórrogas, renovaciones y cambios de nombre; 2) Elaborar, tramitar, solicitar, obtener, realizar, ejecutar y registrar contratos, licencias, autorizaciones y registros de cualesquiera clases; 3) Intervenir como demandante o como demandado en cualquier instancia y recurso y ante cualquier juez, entidad, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía, tales como acciones derivadas de nombre o enseña comerciales; acciones reivindicatorias; acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal, demandas penales y civiles; acciones de indemnización de perjuicios, reclamos, u observaciones a cualquier asunto sobre propiedad intelectual; al ejercicio de medidas cautelares y cualesquiera otras acciones, medidas o recursos similares relacionados con la propiedad intelectual.

A este efecto, lo facultamos para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la Ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores dando al descargo respectivo, y en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros) intereses, con todas las facultades necesarias, y por este documento desde ahora declaro(amos) válido y bueno todo cuanto los apoderados hicieren en mi (nuestro) beneficio.

Este poder comprende la facultad de ratificar, o confirmar en mi (nuestro) nombre lo actuado, así como la facultad de recibir, desistir, transigir, comprometer, sustituir y revocar sustituciones, recibir notificaciones y nombrar apoderados judiciales o extrajudiciales.

Firmado en el de de



NOTARIAL CERTIFICATE (Corporation)

UNITED STATES OF AMERICA)
STATE OF NEW JERSEY) ss.
COUNTY OF SOMERSET)

On this 1st day of March, 2002, personally appeared before me, Ross J. Oehler, Assistant Secretary, known or identified to me to be the individual described in and who executed the foregoing document, **Power of Attorney**, and acknowledged the same as a free act and deed for uses and purposes therein expressed by authority of the said Corporation incorporated under the laws of the State of Delaware, United States of America.

I further certify that said authority, dated November 29, 2000, is based on a Resolution of the Board of Directors of said Corporation, which I have seen, appointing the said individual Attorney-in-fact with full power to sign the foregoing document on behalf of the said Corporation and that the purposes for which said document is granted are within the scope of the objects or activities of said Corporation,

SEAL


Notary Public

Nancy J. Ingram
Notary Public, State of New Jersey
My Commission Expires August 2, 2004

Notary Signature
Print or Type Name
of Notary, Expiration

STATE OF NEW JERSEY }
COUNTY OF SOMERSET. }

ss.:

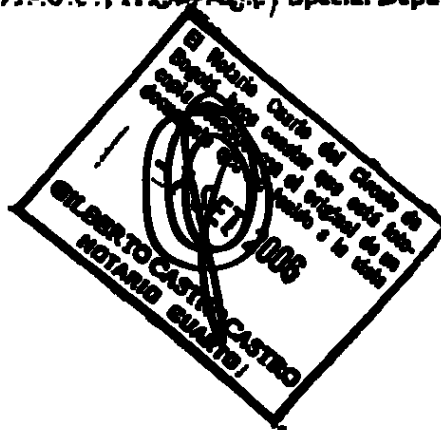
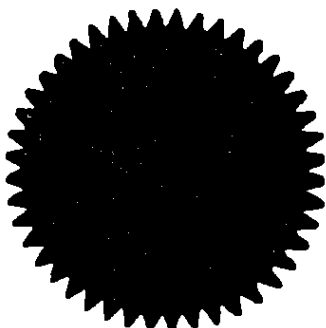
I, PETER R. WIDIN, Clerk of the County of Somerset and also Deputy Clerk of the Superior Court in and for said County, the same being a Court of Record, Do Hereby Certify, that

Nancy J. Ingram
whose name is subscribed to the certificate of acknowledgement, proof or affidavit of the annexed instrument, was at the time of taking such acknowledgement, proof or affidavit, a **NOTARY PUBLIC OF NEW JERSEY**

In and for said State, duly appointed, qualified, commissioned and sworn and authorized by law to take affidavits, acknowledgements or proofs of deeds or conveyances for lands, tenements or hereditaments and other instruments in writing in said State of New Jersey. And I further Certify, that I am well acquainted with the handwriting of said official and verily believe the signature to the said certificate of acknowledgement, proof or affidavit is genuine.

In Testimony Whereof, I have hereunto set my hand and affixed the seal of said County on

APR - 5 2002 R. PETER WIDIN Clerk.
by *Gilberto Castro* Special Deputy Clerk.



8

TRADUCCION OFICIAL DEL INGLES de las certificaciones y la
Apostilla adjuntas al poder que la compañía AVENTIS PHARMACEU-
TICALS INC domiciliada en Bridgewater, New Jersey, E.U.A.,
otorga a Gustavo Hollmann Restrepo y/o Luis Patiño Leyva.

CERTIFICADO NOTARIAL (Sociedad)

ESTADOS UNIDOS DE AMERICA

ESTADO DE NEW JERSEY

CONDADO DE SOMERSET

El día 1° de Marzo del año 2002 ante la suscrita Notaria com-
pareció personalmente Ross J. Oehler, Secretario Suplente,
quien yo sé o quien comprobó ante mí que es la persona mencio-
nada en el adjunto poder y quien lo ejecutó, y él reconoció
haber ejecutado dicho instrumento como un acto libre y volun-
tario destinado para los usos y propósitos allí expresados en
virtud a la autoridad que le concede la mencionada sociedad,
la cual está incorporada de conformidad con las leyes del Es-
tado de Delaware, Estados Unidos de América.

Certifico además que dicha autoridad, fechada el 29 de Noviem-
bre del 2000, se basa en una resolución de la Junta de Direc-
tores de la mencionada sociedad, documento que yo he tenido a
la vista, nombrando a la mencionada persona apoderado con todo
poder para firmar el instrumento adjunto en nombre de dicha
sociedad, y que los propósitos para los cuales se otorga dicho
instrumento se encuentran dentro del alcance de los negocios
o actividades de la mencionada corporación.

Nancy J. Ingram

Notaria Pública del Estado de New Jersey

Mi comisión expira Agosto 2 del 2004

(Firma y Sello Oficial)



ESTADO DE NEW JERSEY, CONDADO DE SOMERSET

Yo, Peter S. Widin, Secretario del Condado de Somerset y Secretario Suplente de la Corte Superior de dicho Condado, la cual es una Corte de Registro, certifico que Nancy J. Ingram, cuyo nombre aparece suscrito al certificado de reconocimiento, prueba o declaración del instrumento adjunto, era en el momento de tomar tal reconocimiento, prueba o declaración Notaria Pública en y para el Estado de New Jersey, debidamente nombrada, calificada, comisionada y juramentada y autorizada por la ley para tomar declaraciones, reconocimientos o pruebas de escrituras o traspasos de tierras, tenencias o herencias y otros instrumentos escritos en el mencionado Estado. Y certifico además que conozco bien la firma de dicha funcionaria y estoy convencido de que la firma que aparece en el mencionado certificado de reconocimiento, prueba o declaración es genuina.

En testimonio de lo cual coloco mi firma y el sello del Condado el día de hoy 5 de Abril del 2002.

R. Peter Widin, Secretario

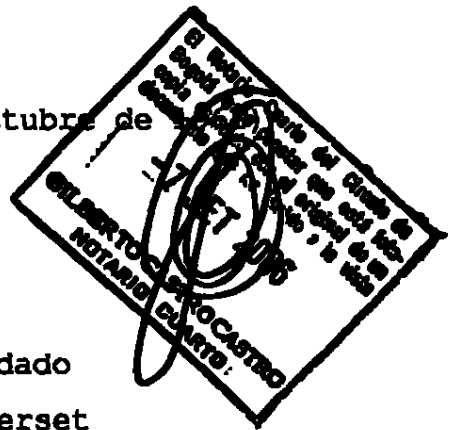
Deborah L. Anderson, Secretaria Especial Suplente

(Firma y Sello Oficial)

APOSTILLA

(Convención de La Haya del 5 de Octubre de 1961)

1. País: Estados Unidos de América
Este documento público
2. Ha sido firmado por: R. Peter Widin
3. En su calidad de: Secretario del Condado
4. Y lleva el sello: del Condado de Somerset



Confirmado

5. En: Trenton, New Jersey
6. El día: Abril 9/2002
7. Por: John E. McCormac, CPA, Tesorero de New Jersey
8. Bajo el No.: A149012
9. Sello: Secretaría de Estado de New Jersey
10. Firma: (ilegible)

M. Méndez S.

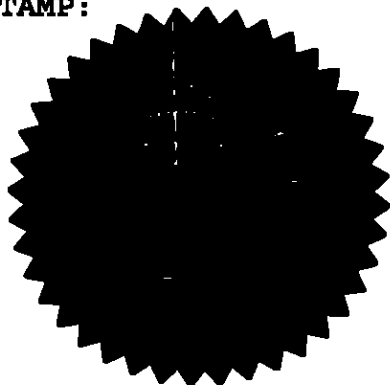
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
NANCY J INGRAM
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
NANCY J INGRAM, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 7TH DAY OF SEPTEMBER 2006
7. BY: Bradley Abelow, NEW JERSEY TREASURER
8. NO. A270168
9. SEAL/STAMP:
10. SIGNATURE



Bradley Abelow

4

NOTARIAL TRUE COPY

UNITED STATES OF AMERICA)
STATE OF NEW JERSEY) ss.
COUNTY OF SOMERSET)

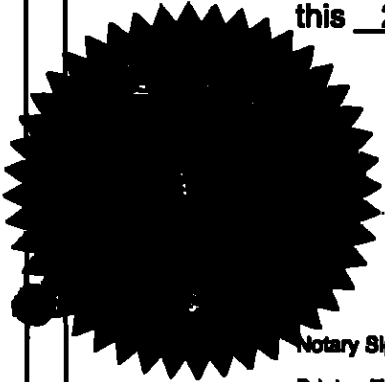
TO ALL TO WHOM THESE PRESENTS SHALL COME,

I Do Hereby Certify under the Oath of my Office and Seal that the annexed document(s) are TRUE COPIES of the original document(s) which I have compared.

IN TESTIMONY WHEREOF, I have hereunto set my hand and affixed the Seal under the Oath of my Office

At Bridgewater, New Jersey, United States of America

this 29th day of August, 2006.



Notary Signature

Print or Type Name
of Notary, Expiration
Date, if any, Title or
Jurisdiction Area

Nancy J. Ingram
Notary Public
Nancy J. Ingram
Notary Public, State of New Jersey
My Commission Expires August 2, 2009

Docket No. USAV2003/0122 CO PCT



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231



700088521A

JUNE 23, 2004

PTAS

AVENTIS PHARMACEUTICALS INC.
JOSEPH STRUPCZEWSKI
ROUTE 202-206
P.O. BOX 6800
BRIDGEWATER, NJ 08807-0800

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT DIVISION, BOX ASSIGNMENTS, CG-4, 1213 JEFFERSON DAVIS HWY, SUITE 320, WASHINGTON, D.C. 20231.

RECORDATION DATE: 06/23/2004

REEL/FRAME: 014767/0714
NUMBER OF PAGES: 3

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:

MCGARRY, DANIEL G.

DOC DATE: 05/17/2004

ASSIGNOR:

CHANDROSS, KAREN

DOC DATE: 05/13/2004

ASSIGNOR:

MERRILL, JEAN

DOC DATE: 05/16/2004

ASSIGNEE:

AVENTIS PHARMACEUTICALS INC.
300 SOMERSET CORPORATE BOULEVARD
BRIDGEWATER, NEW JERSEY 08807

014767/0714 PAGE 2

SERIAL NUMBER: 60558419

FILING DATE: 04/01/2004

PATENT NUMBER:

ISSUE DATE:

TITLE: 1, 3, 4-OXADIAZOL-2-ONES AS PPAR DELTA MODULATORS AND THEIR USE
THEREOF

SAUNDRA BALLENGER, EXAMINER
ASSIGNMENT DIVISION
OFFICE OF PUBLIC RECORDS

FORM PTO-1595
1-91-92
(modified)

RECORDATION FORM COVER SHEET
PATENTS ONLY

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

I hereby certify that this correspondence is being transmitted via facsimile to the Commissioner for Patents, Alexandria, VA 22313-1480, Patent and Trademark Assignment System, at (703) 306-6995, on
Date 6/23/04

Signature

M. P. O'Meara

To the Commissioner of Patents. Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

1. Daniel G. MCGARRY
2. Karen CHANDROSS
3. Jean MERRILL

Additional name(s) of conveying party(ies) attached? ☐ YES ☒ NO

2. Name and address of receiving party(ies):

Name: Aventis Pharmaceuticals Inc.
Internal Address:
Street Address: 300 Somerset Corporate Boulevard
City: Bridgewater State: NJ ZIP: 08807

Additional name(s) and address(es) attached? ☐ YES ☒ NO

3. Nature of Conveyance:

☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other

Execution Date: 1. 05/17/04 2. 05/13/04 3. 05/16/04

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s): 60558,419

B. Patent No.(s):

Additional numbers attached? ☐ YES ☒ NO

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Joseph Strupczewski, Reg. No. 50,903
Internal Address: Aventis Pharmaceuticals Inc.
Street Address: Route 202-206 / P.O. Box 6800
City: Bridgewater State: NJ ZIP: 08807-6800
** FAX NUMBER: (908) 231-2828 **
Our Reference No.: USAV2003/0123 US P&P

6. Total number of applications and patents involved: 1

7. Total (\$7 CFR 3.41): \$40.00

☐ Enclosed
☒ Authorized to be charged to deposit account

8. Deposit account number: 18-1982

DO NOT USE THIS SPACE

8. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Joseph Strupczewski, Reg. No. 50,903
Name of Person Signing

Joseph Strupczewski
Signature

Date: 06/23/2004

Total number of pages comprising cover sheet:

OMB No. 0851-0011 (exp. 4/04)

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Mail documents to be recorded with required cover sheet information to:
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ASSIGNMENT AND AGREEMENT

For value received and intending to be legally bound, I/we, the undersigned joint inventor(s) (Assignor(s)), sell, assign and transfer to Aventis Pharmaceuticals Inc. (Assignee), 300 Somerset Corporate Boulevard, Bridgewater, New Jersey 08807-2854, United States of America, and its successors, assigns and legal representatives, the entire right, title and interest in and to my/our invention and any improvements thereon for all countries of the world, relating in and to the application for United States Letters Patent therefor, assigned Attorney Docket No. USAV2003/0122 US PSP and (if filed prior to the execution hereof) filed on April 1, 2004, as Serial No. 60/558,419, entitled

1,3,4-OXADIAZOL-2-ONES AS PPAR DELTA MODULATORS AND THEIR USE THEREOF

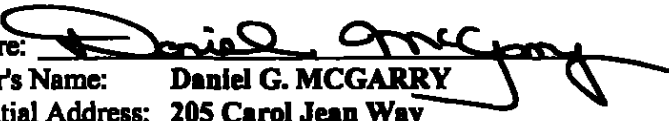
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I/we covenant with said assignee, its successors, assigns and legal representatives, that the rights and property herein conveyed are free and clear of any encumbrance, and that I/we have full right to convey the same as herein expressed.

Signed at Bridgewater on this 17th day of May, 2004.
(City, State and Nation)

Signature: 

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Signed at Bridgewater NJ USA on this 16 day of May, 2004.
(City, State and Nation)

Signature: Jean Merrill
Inventor's Name: **Jean MERRILL**
Residential Address: **101 Alpine Lane**
Whippany, NJ 07981



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JOSEPH STRUPCZEWSKI
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- ASSIGNOR:

KEIL, STEFANIE

DOC DATE: 05/14/2004

ASSIGNOR:

WENDLER, WOLFGANG

DOC DATE: 05/17/2004

ASSIGNEE:

AVENTIS PHARMA DEUTSCHLAND GMBH
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Name: Aventis Pharma Deutschland GmbH
Internal Address:
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City: Frankfurt am Main State: Germany ZIP: 65926

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Name: Joseph Strupczewski, Reg. No. 50,903
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City: Bridgewater State: NJ ZIP: 08807-4800
** FAX NUMBER: (908) 221-2628 **
Our Reference No.: USAV2003/0122 US PGP

6. Total number of applications and patents involved: 1

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For value received and intending to be legally bound, I/we, the undersigned joint inventor(s) (Assignor(s)), sell, assign and transfer to Aventis Pharma Deutschland GmbH (Assignee), Industriepark Hoechst, Frankfurt am Main, 65926 Germany and its successors, assigns and legal representatives, the entire right, title and interest in and to my/our invention and any improvements thereon for all countries of the world, relating in and to the application for United States Letters Patent therefor, assigned Attorney Docket No. USAV2003/0122 US PSP and (if filed prior to the execution hereof) filed on April 1, 2004, as Serial No. 60/558,419, entitled

1,3,4-OXADIAZOL-2-ONES AS PPAR DELTA MODULATORS AND THEIR USE THEREOF

and all the rights and privileges, including any and all benefits under the International Convention for the Protection of Industrial Property, including the right to claim priority based on said United States application, and under any and all Letters Patent which may be granted therefor, and all right, title and interest in and to every patent application filed or to be filed on said invention in any other country or patent organization, including continuations, divisions, renewals, revivals, and any substitute applications of said United States application, and any and all patents which may issue thereon, and any reissues, pipelines and extensions, and governmental exclusivity rights of the same.

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Signed at Frankfurt, Germany on this 13th day of May, 2004.
(City, State and Nation)

Signature: Jochen Goerlitz
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Signed at Frankfurt, Germany on this 14th day of May, 2004.
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Signature: Stefanie Keil
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Signed at Frankfurt, Germany on this 17th day of May, 2004.
(City, State and Nation)

Signature: Wolfgang Wendler
Inventor's Name: **Wolfgang WENDLER**
Residential Address: **Hsintchener Str. 12a**
65618 Selters (Germany)



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ASSIGNOR:

AVENTIS PHARMA DEUTSCHLAND GMBH

DOC DATE: 06/14/2004

ASSIGNEE:

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SERIAL NUMBER: 60558419

FILING DATE: 04/01/2004

PATENT NUMBER:

ISSUE DATE:

TITLE: 1, 3, 4-OXADIAZOL-2-ONES AS PPAR DELTA MODULATORS AND THEIR USE
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Name: Joseph Strupczewski, Reg. No. 50,903

Internal Address: Aventis Pharmaceuticals Inc.

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City: Bridgewater State: NJ ZIP: 08807-6800

** FAX NUMBER: (908) 231-2626 **

Our Reference No.: USA V2003/0123 US PST

6. Total number of applications and patents involved: 1

7. Total (37 CFR 3.41): \$40.00

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**1,3,4-OXADIAZOL-2-ONES AS PPAR DELTA MODULATORS
AND THEIR USE THEREOF**

and all the rights and privileges, including any and all benefits under the International Convention for the Protection of Industrial Property, including the right to claim priority based on said priority applications, and under any and all Letters Patent which may be granted therefore, and all right, title and interest in and to every patent application filed or to be filed on said invention in any other country or patent organization, including continuations, divisions, renewals, revivals, and any substitute applications of the above applications, and any and all patents which may issue thereon, and any reissues, pipelines and extensions, and governmental exclusivity rights of the same.

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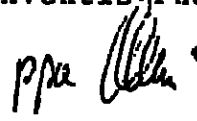
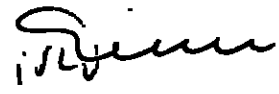
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Signed at Frankfurt, Germany on this 14th day of June, 2004
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Aventis Pharma Deutschland GmbH

By:

 
Name(s): Elmar-Michael Wein Hans-Jürgen
Title : Prokurist Handlungsbevollmächtigter

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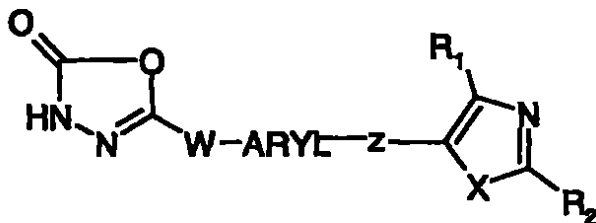
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(54) Title: 1,3,4-OXADIAZOL-2-ONES AS PPAR DELTA MODULATORS AND THEIR USE THEREOF



(I)

(57) Abstract: The present invention is directed to 1, 3, 4-oxadiazolones, compounds of formula (I) and their pharmaceutically acceptable salts stereoisomers, tautomers, or solvates thereof. Novel compounds include those of formula (I), in which radicals are as defined herein. The compounds of this invention are modulators of PPARdelta and therefore useful as pharmaceutical agents, especially for the treatment of demyelinating diseases and disorders of fatty acid metabolism and glucose utilization.

WO 2005/097762 A2

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10 **1, 3, 4-OXADIAZOL-2-ONES AS PPAR DELTA MODULATORS AND THEIR USE**
THEREOF

FIELD OF THE INVENTION

15 This invention relates to novel compounds and pharmaceutical formulations that act as selective PPARdelta ligand receptor binders, which are useful in modulating PPARdelta receptors for the treatment of diseases mediated by nuclear hormone receptors. The PPARdelta ligand receptor binders of this invention are useful as agonists or antagonists of the PPARdelta receptor.

20 **BACKGROUND OF THE INVENTION**

The peroxisome proliferator-activated receptors (PPARs) comprise a subfamily of the nuclear receptor superfamily. Four closely related isoforms have been identified and cloned and are commonly known as PPARalpha, PPARGamma-1, PPARGamma-2 and PPARdelta. Each receptor subtype has a signature DNA binding domain (DBD) and a ligand-binding domain (LBD), both being necessary for ligand activated gene expression. PPARs bind as heterodimers with a retinoid X receptor. See J. Berger and D. E. Miller, *Annu. Rev. Med.*, 2002, 53, 409-435.

25 PPARdelta (also known as PPARbeta) is expressed in a broad range of mammalian tissue, but little information regarding its biological functions or the full array of genes regulated by the receptor have been elucidated. However, it has recently been found that agonists may be useful to treat conditions such as dyslipidemia and certain dermatological conditions, while antagonists may be useful to treat osteoporosis or colorectal cancer (D.

30

Sternbach, in *Annual Reports in Medicinal Chemistry, Volume 38*, A. M. Doherty, ed., Elsevier Academic Press, 2003 pp. 71-80).

PPARdelta appears to be significantly expressed in the CNS; however much of its function there still remains undiscovered. Of singular interest however, is the discovery that PPARdelta was expressed in rodent oligodendrocytes, the major lipid producing cells of the CNS (J. Granneman, et al., *J. Neurosci. Res.*, 1998, 51, 563-573). Moreover, it was also found that a PPARdelta selective agonist was found to significantly increase oligodendroglial myelin gene expression and myelin sheath diameter in mouse cultures (I. Saluja et al., *Glia*, 2001, 33, 194-204). Thus, PPARdelta activators may be of use for the treatment of demyelinating and dysmyelinating diseases.

Demyelinating conditions are manifested in loss of myelin- the multiple dense layers of lipids and protein which cover many nerve fibers. These layers are provided by oligodendroglia in the central nervous system (CNS), and Schwann cells in the peripheral nervous system (PNS). In patients with demyelinating conditions, demyelination may be irreversible; it is usually accompanied or followed by axonal degeneration, and often by cellular degeneration. Demyelination can occur as a result of neuronal damage or damage to the myelin itself--whether due to aberrant immune responses, local injury, ischemia, metabolic disorders, toxic agents, or viral infections (Prineas and McDonald, *Demyelinating Diseases. In Greenfield's Neuropathology*, 6.sup.th ed. (Edward Arnold: New York, 1997) 813-811, Beers and Berkow, eds., *The Merck Manual of Diagnosis and Therapy*, 17.sup.th ed. (Whitehouse Station, N.J.: Merck Research Laboratories, 1999) 1299, 1437, 1473-76, 1483).

Central demyelination (demyelination of the CNS) occurs in several conditions, often of uncertain etiology, that have come to be known as the primary demyelinating diseases. Of these, multiple sclerosis (MS) is the most prevalent. Other primary demyelinating diseases include adrenoleukodystrophy (ALD), adrenomyeloneuropathy, AIDS-vacuolar myelopathy, HTLV-associated myelopathy, Leber's hereditary optic atrophy, progressive multifocal leukoencephalopathy (PML), subacute sclerosing panencephalitis, Guillian-Barre syndrome and tropical spastic paraparesis. In addition, there are acute conditions in which demyelination can occur in the CNS, e.g., acute disseminated encephalomyelitis (ADEM) and acute viral encephalitis. Furthermore, acute transverse myelitis, a syndrome in which an acute spinal cord transection of unknown cause affects both gray and white matter in one or more adjacent thoracic segments, can also result in demyelination. Also, disorders in which myelin forming glial cells are damaged including spinal cord injuries, neuropathies and nerve injury.

Selective PPARdelta modulators may also be useful for treating or preventing other disease states see, for example, Joel Berger et al., Annu. Rev. Med. 2002, 53, 409 – 435; Timothy Wilson et al. J. Med. Chem., 2000, Vol. 43, No. 4, 527-550; Steven Klierer et al., Recent Prog Horm Res. 2001; 56: 239-63; Jean-Charles Fruchart, Bart Staels and Patrick Duriez: PPARs, Metabolic Disease and Arteriosclerosis, Pharmacological Research, Vol. 44, No. 5, 345-52; 2001; Sander Kersten, Beatrice Desvergne & Walter Wahli: Roles of PPARs in health and disease, Nature, vol 405, 25 may 2000; 421-4; Ines Pineda Torra, Giulia Chinetti, Caroline Duval, Jean-Charles Fruchart and Bart Staels: Peroxisome proliferator-activated receptors: from transcriptional control to clinical practice, Curr Opin Lipidol 12: 2001, 245-254).

Compounds acting as PPARdelta modulators may be particularly suitable for the treatment and/or prevention of disorders of fatty acid metabolism and glucose utilization disorders in which insulin resistance is involved.

Diabetes mellitus, especially type 2 diabetes, including the prevention of the sequelae associated therewith. Particular aspects in this connection are hyperglycemia, improvement in insulin resistance, improvement in glucose tolerance, protection of the pancreatic B cells, prevention of macro- and microvascular disorders.

Dyslipidemias and their sequelae such as, for example, atherosclerosis, coronary heart disease, cerebrovascular disorders etc, especially those (but not restricted thereto) which are characterized by one or more of the following factors: high plasma triglyceride concentrations, high postprandial plasma triglyceride concentrations, low HDL cholesterol concentrations, low ApoA lipoprotein concentrations, high LDL cholesterol concentrations, small dense LDL cholesterol particles, high ApoB lipoprotein concentrations.

Various other conditions which may be associated with the metabolic syndrome, such as: obesity (excess weight), including central obesity, thromboses, hypercoagulable and prothrombotic states (arterial and venous), high blood pressure, heart failure such as, for example (but not restricted thereto), following myocardial infarction, hypertensive heart disease or cardiomyopathy.

Other disorders or conditions in which inflammatory reactions or cell differentiation, may for example be involved are: atherosclerosis such as, for example (but not restricted thereto), coronary sclerosis including angina pectoris or myocardial infarction, stroke, vascular restenosis or reocclusion, chronic inflammatory bowel diseases, such as, for example,

Crohn's disease and ulcerative colitis, pancreatitis, other inflammatory states, retinopathy, adipose cell tumors, lipomatous carcinomas such as, for example, liposarcomas, solid tumors and neoplasms such as, for example (but not restricted thereto), carcinomas of the gastrointestinal tract, of the liver, of the biliary tract and of the pancreas, endocrine tumors, carcinomas of the lungs, of the kidneys and the urinary tract, of the genital tract, prostate carcinomas etc., acute and chronic myeloproliferative disorders and lymphomas angiogenesis, neurodegenerative disorders, Alzheimer's disease, Parkinson's disease, erythematous squamous dermatoses such as, for example, psoriasis, acne vulgaris.

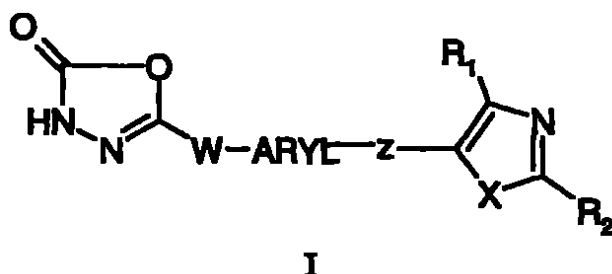
Other skin disorders and dermatological conditions modulated by PPARdelta:

- eczemas and neurodermitis, dermatitis such as, for example, seborrheic dermatitis or photodermatitis, keratitis and keratoses such as, for example, seborrheic keratoses, senile keratoses, actinic keratosis, photo-induced keratoses or keratosis follicularis keloids and keloid prophylaxis, warts, including condylomata or condylomata acuminata, human papilloma viral (HPV) infections such as, for example, venereal papillomata, viral warts such as, for example, molluscum contagiosum, leukoplakiapapular dermatoses such as, for example, Lichen planus, skin cancer such as, for example, basal-cell carcinomas, melanomas or cutaneous T-cell lymphomas, localized benign epidermal tumors such as, for example, keratoderma, epidermal naevi and chilblains.

Various other conditions potentially modulated by PPARdelta including syndrome X, polycystic ovary syndrome (PCOS), asthma osteoarthritis, lupus erythematosus (LE) or inflammatory rheumatic disorders such as, for example, rheumatoid arthritis, vasculitis, wasting (cachexia), gout ischemia/reperfusion syndrome and acute respiratory distress syndrome (ARDS).

SUMMARY OF THE INVENTION

The present invention is directed to compound of formula I.



wherein

ARYL is phenyl or pyridinyl, wherein said phenyl or pyridinyl is optionally substituted with one or more substituents selected from the group consisting of halogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, C₁₋₆perfluoroalkyl; C₁₋₆alkylthio, hydroxy, hydroxyC₁₋₆alkyl, C₁₋₆acyloxy, nitro, cyano, C₁₋₆alkylsulfonyl, amino, C₁₋₆alkylamino and C₁₋₆alkoxycarbonyl;

W is a bond or (CH₂)_m, wherein m is an integer from 1 to 4;

Z is -O(CH₂)_n-, -SO₂(CH₂)_n-, -(CH₂)_n-Y-(CH₂)_n-, -(CH₂)_n-CO-, -O(CH₂)_n-CO- or -(CH₂)_n-Y-(CH₂)_n-CO- wherein Y is NR₃, O or S and R₃ is selected from the group consisting of H, C₁₋₆alkyl, C₃₋₈cycloalkyl, C₁₋₆alkylC₃₋₈cycloalkyl and benzyl and n is independently an integer from 1 to 5;

X is NR₃, O or S wherein R₃ is as defined above;

R₁ is H, halogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆perfluoroalkyl; hydroxyC₁₋₆alkyl, nitro, cyano, and C₁₋₆alkylamino; and

R₂ is substituted or unsubstituted phenyl, pyridinyl or thienyl wherein the substituents are selected from the group consisting of halogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, C₁₋₆perfluoroalkyl, C₁₋₆alkylthio, hydroxy, hydroxyC₁₋₆alkyl, C₁₋₆acyloxy, nitro, cyano, C₁₋₆alkylsulfonyl, amino, C₁₋₆alkylamino and C₁₋₆alkoxycarbonyl; or a stereoisomer, a tautomer or a solvate thereof or a pharmaceutically acceptable salt thereof.

The present invention is also directed to pharmaceutical compositions of formula I, and methods of using said compounds and compositions for modulating PPARdelta in a subject in need of such modulation by administering a compound which preferentially modulates the activity of PPARdelta. The present compounds possess useful PPARdelta modulating activity, and are expected to be useful in the treatment or prophylaxis of a disease or condition in which said disease is capable of being treated by modulation of PPARdelta ligand binding activity, by administering to the patient a therapeutically effective amount of the compound of formula I.

DETAILED DESCRIPTION OF THE INVENTION

The terms as used herein have the following meanings:

As used herein, the expression "C₁₋₆ alkyl" includes methyl and ethyl groups, and straight-chained or branched propyl, butyl, pentyl and hexyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and tert-butyl. Derived expressions such as "C₁₋

alkoxy", "C₁₋₆alkoxyC₁₋₆alkyl", "hydroxyC₁₋₆alkyl", "C₁₋₆alkylcarbonyl", "C₁₋₆alkoxycarbonylC₁₋₆alkyl", "C₁₋₆alkoxycarbonyl", "aminoC₁₋₆alkyl", "C₁₋₆alkylcarbamoylC₁₋₆alkyl", "C₁₋₆dialkylcarbamoylC₁₋₆alkyl" "mono- or di-C₁₋₆alkylaminoC₁₋₆alkyl", aminoC₁₋₆alkylcarbonyl", "diphenylC₁₋₆alkyl", "arylC₁₋₆alkyl", "arylcarbonylC₁₋₆alkyl" and "aryloxyC₁₋₆alkyl" are to be construed accordingly.

As used herein, the expression "C₂₋₆alkenyl" includes ethenyl and straight-chained or branched propenyl, butenyl, pentenyl and hexenyl groups. Similarly, the expression "C₂₋₆alkynyl" includes ethynyl and propynyl, and straight-chained or branched butynyl, pentynyl and hexynyl groups.

As used herein "aryl" represents a carbocyclic aromatic ring system such as phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, pentalenyl, azulenyl, biphenylenyl and the like. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic aromatic systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl and the like.

As used herein "aryloxy" represents a group —O-aryl wherein aryl is as defined above.

As used herein "heteroaryl" (on its own or in any combination, such as "heteroaryloxy", or "heteroaryl alkyl")—a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazolinyl, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, tetrazole, triazole, imidazole, or benzimidazole.

As used herein "heterocyclic or heterocyclyl" (on its own or in any combination, such as "heterocyclylalkyl")—a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, tetrahydro pyran, or imidazolidine.

As used herein, the expression "C₁₋₆ perfluoroalkyl" means that all of the hydrogen atoms in said alkyl group are replaced with fluorine atoms. Illustrative examples include trifluoromethyl and pentafluoroethyl, and straight-chained or branched heptafluoropropyl, nonafluorobutyl, undecafluoropentyl and tridecafluorohexyl groups. Derived expression, "C₁₋₆ perfluoroalkoxy", is to be construed accordingly.

As used herein, the expression "C₃₋₈cycloalkyl" means cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein, the expression "C₃₋₈cycloalkylC₁₋₆alkyl" means that the C₃₋₈cycloalkyl as defined herein is further attached to C₁₋₆alkyl as defined herein. Representative examples include cyclopropylmethyl, 1-cyclobutylethyl, 2-cyclopentylpropyl, cyclohexylmethyl, 2-cycloheptylethyl and 2-cyclooctylbutyl and the like.

As used herein "halogen" or "halo" means chloro, fluoro, bromo, and iodo.

As used herein "C₁₋₆alkylsulfonyl" in the present context designates a group —S(=O)₂C₁₋₆alkyl wherein C₁₋₆alkyl is as defined above. Representative examples include, but are not limited to, methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, butylsulfonyl, iso-butylsulfonyl, sec-butylsulfonyl, tert-butylsulfonyl, n-pentylsulfonyl, isopentylsulfonyl, neopentylsulfonyl, tert-pentylsulfonyl, n-hexylsulfonyl, isohexylsulfonyl and the like.

As used herein "arylsulfonyl" represents a group —S(=O)₂aryl wherein aryl is as defined above.

As used herein "heteroarylsulfonyl" represents a group —S(=O)₂heteroaryl wherein heteroaryl is as defined above.

The expression "stereoisomers" is a general term used for all isomers of the individual molecules that differ only in the orientation of their atoms in space. Typically it includes mirror image isomers that are usually formed due to at least one asymmetric center, (enantiomers). Where the compounds according to the invention possess two or more asymmetric centers, they may additionally exist as diastereoisomers, also certain individual molecules may exist as geometric isomers (cis/trans). It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

"Substituted" means substituted by 1 to 2 substituents independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ perfluoroalkyl, hydroxy, -CO₂H, an ester, an amide, C₁-C₆ alkoxy, C₁-C₆ perfluoroalkoxy, -NH₂, Cl, Br, I, F, -NH-lower alkyl, and -N(lower alkyl)₂.

The compounds and salts of the present invention may exist in several tautomeric forms, including the enol and imine form, and the keto and enamine form and geometric isomers and mixtures thereof. All such tautomeric forms are included within the scope of the present invention. Tautomers exist as mixtures of a tautomeric set in solution. In solid form,

usually one tautomer predominates. Even though one tautomer may be described, the present invention includes all tautomers of the present compounds.

As used herein the term "modulator" refers to a chemical compound with capacity to either enhance (e.g., "agonist" activity) or inhibit (e.g., "antagonist" activity) a functional property of biological activity or process (e.g., enzyme activity or receptor binding); such enhancement or inhibition may be contingent on the occurrence of a specific event, such as activation or repression of a signal transduction pathway and/or may be manifest only in particular cell types and may result in a measurable biological change.

As used herein, "patient" means a warm blooded animal, such as for example rat, mice, dogs, cats, guinea pigs, and primates such as humans.

As used herein, the expression "pharmaceutically acceptable carrier" means a non-toxic solvent, dispersant, excipient, adjuvant, or other material which is mixed with the compound of the present invention in order to permit the formation of a pharmaceutical composition, i.e., a dosage form capable of administration to the patient. One example of such a carrier is a pharmaceutically acceptable oil typically used for parenteral administration.

The term "pharmaceutically acceptable salts" as used herein means that the salts of the compounds of the present invention can be used in medicinal preparations. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, 2-hydroxyethanesulfonic acid, p-toluenesulfonic acid, fumaric acid, maleic acid, hydroxymaleic acid, malic acid, ascorbic acid, succinic acid, glutaric acid, acetic acid, salicylic acid, cinnamic acid, 2-phenoxybenzoic acid, hydroxybenzoic acid, phenylacetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, glycolic acid, lactic acid, pyruvic acid, malonic acid, carbomic acid or phosphoric acid. The acid metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate can also be formed. Also, the salts so formed may present either as mono- or di- acid salts and can exist either as hydrated or can be substantially anhydrous. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

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The term "therapeutically effective amount" as used herein means an amount of the compound which is effective in treating the named disorder or condition.

The invention also provides pharmaceutical compositions comprising one or more of the compounds according to this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation.

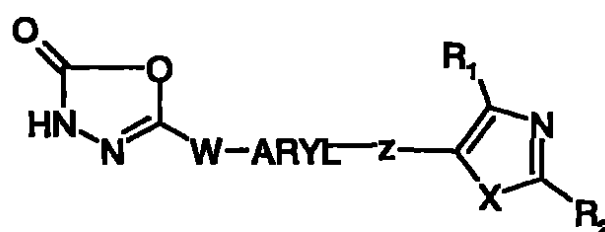
Alternatively, the compositions may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. An erodible polymer containing the active ingredient may be envisaged. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Flavored unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer, which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of various disease states as described herein, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 20 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

As used in the examples and preparations that follow, the terms used therein shall have the meanings indicated: "kg" refers to kilograms, "g" refers to grams, "mg" refers to milligrams, "μg" refers to micrograms, "pg" refers to picograms, "mol" refers to moles, "mmol" refers to millimoles, "nmole" refers to nanomoles, "L" refers to liters, "mL" or "ml" refers to milliliters, "μL" refers to microliters, "°C" refers to degrees Celsius, "R_f" refers to retention factor, "mp" or "m.p." refers to melting point, "dec" refers to decomposition, "bp" or "b.p." refers to boiling point, "mm of Hg" refers to pressure in millimeters of mercury, "cm" refers to centimeters, "nm" refers to nanometers, "[α]_D²⁰" refers to specific rotation of the D line of sodium at 20°C obtained in a 1 decimeter cell, "c" refers to concentration in g/mL, "THF" refers to tetrahydrofuran, "DMF" refers to dimethylformamide, "NMP" refers to 1-methyl-2-pyrrolidinone, "brine" refers to a saturated aqueous sodium chloride solution, "M" refers to molar, "mM" refers to millimolar, "μM" refers to micromolar, "nM" refers to nanomolar, "TLC" refers to thin layer chromatography, "HPLC" refers to high performance liquid chromatography, "HRMS" refers to high resolution mass spectrum, "CIMS" refers to chemical ionization mass spectrometry, "ESI" refers to electrospray ionization mass spectrometry, "t_R" refers to retention time, "lb" refers to pounds, "gal" refers to gallons, "L.O.D." refers to loss on drying, "μCi" refers to microcuries, "i.p." refers to intraperitoneally, "i.v." refers to intravenously.

In one aspect of this invention there is disclosed novel compounds having the general structure shown in formula I:



wherein

ARYL is phenyl or pyridinyl, wherein said phenyl or pyridinyl is optionally substituted with one or more substituents selected from the group consisting of halogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, C₁₋₆perfluoroalkyl; C₁₋₆alkylthio, hydroxy, hydroxyc₁₋₆alkyl, C₁₋₆acyloxy, nitro, cyano, C₁₋₆alkylsulfonyl, amino, C₁₋₆alkylamino and C₁₋₆alkoxycarbonyl;

W is a bond or (CH₂)_m, wherein m is an integer from 1 to 4;

Z is -O(CH₂)_n-, -SO₂(CH₂)_n-, -(CH₂)_n-Y-(CH₂)_n-, -(CH₂)_n-CO-, -O(CH₂)_n-CO- or -(CH₂)_n-Y-(CH₂)_n-CO- wherein Y is NR₃, O or S and R₃ is selected from the group consisting of H, C₁₋₆alkyl, C₃₋₈cycloalkyl, C₁₋₆alkylC₃₋₈cycloalkyl and benzyl and n is independently an integer from 1 to 5;

X is NR₃, O or S wherein R₃ is as defined above;

R₁ is H, halogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆perfluoroalkyl; hydroxyc₁₋₆alkyl, nitro, cyano, and C₁₋₆alkylamino; and

R₂ is substituted or unsubstituted phenyl, pyridinyl or thienyl wherein the substituents are selected from the group consisting of halogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, C₁₋₆perfluoroalkyl, C₁₋₆alkylthio, hydroxy, hydroxyc₁₋₆alkyl, C₁₋₆acyloxy, nitro, cyano, C₁₋₆alkylsulfonyl, amino, C₁₋₆alkylamino and C₁₋₆alkoxycarbonyl; or a stereoisomer, a tautomer or a solvate thereof or a pharmaceutically acceptable salt thereof.

In a further aspect of this embodiment, is disclosed a compound wherein ARYL is phenyl.

Compounds exemplary of this embodiment are selected from the group consisting of:

5-[4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl]-3H-[1,3,4]oxadiazol-2-one, 5-[4-(4-methyl-2-*m*-tolyl-oxazol-5-ylmethoxy)-phenyl]-3H-[1,3,4]oxadiazol-2-one, 5-[4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl)-methoxymethyl]-phenyl]-3H-[1,3,4]oxadiazol-2-one, 5-[3-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl)-methoxymethyl]-phenyl]-3H-[1,3,4]oxadiazol-2-one, 5-[4-[4-butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-chloro-phenyl]-3H-[1,3,4]oxadiazol-2-

one, 5-{4-[4-butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxymethyl]-2-fluoro-phenyl}-3H-[1,3,4]oxadiazol-2-one, 5-{4-[4-butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzyl}-3H-[1,3,4]oxadiazol-2-one, and 5-(2-{3-[4-butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-ethyl)-3H-[1,3,4]oxadiazol-2-one.

5 In another aspect of this embodiment, is disclosed a compound wherein ARYL is phenyl and R₂ is phenyl.

In a further aspect of this embodiment, is disclosed a compound wherein ARYL is phenyl, Z is -O(CH₂)_n- and R₂ is phenyl.

10 In yet another aspect of this embodiment, is disclosed a compound wherein ARYL is phenyl, Z is -O(CH₂)_n-, X is O or S and R₂ is phenyl.

In another aspect of this embodiment, is disclosed a compound wherein ARYL is phenyl, Z is -O(CH₂)_n-, X is O or S, R₁ is C₁₋₆alkyl and R₂ is phenyl and W is a bond.

In a further aspect of this embodiment, is disclosed a compound wherein X is O.

In yet another aspect of this embodiment, is disclosed a compound wherein X is S.

15 In a further aspect of this embodiment, is disclosed a compound wherein ARYL is phenyl, Z is -(CH₂)_n-Y-(CH₂)_n- and R₂ is phenyl.

In yet another aspect of this embodiment, is disclosed a compound wherein ARYL is phenyl, Z is -(CH₂)_n-Y-(CH₂)_n-, X is O or S and R₂ is phenyl.

20 In another aspect of this embodiment, is disclosed a compound wherein ARYL is phenyl, Z is -(CH₂)_n-Y-(CH₂)_n-, X is O or S, R₁ is C₁₋₆alkyl and R₂ is phenyl and W is a bond.

In yet another aspect of this embodiment, is disclosed a compound wherein X is S.

In another aspect of this embodiment, is disclosed a compound wherein Y is O.

In a further aspect of this embodiment, is disclosed a compound wherein ARYL is phenyl, Z is -O(CH₂)_n- and R₂ is phenyl.

25 In yet another aspect of this embodiment, is disclosed a compound wherein ARYL is phenyl, Z is -O(CH₂)_n-, X is O or S and R₂ is phenyl, R₁ is C₁₋₆alkyl and R₂ is phenyl and W is (CH₂)_m wherein m is an integer from 1 to 4..

In yet another aspect of this embodiment, is disclosed a compound wherein X is S.

30 In another embodiment of the present invention, is disclosed a pharmaceutical composition comprising an effective amount of a compound of formula I and a pharmaceutical acceptable carrier.

In another embodiment of the present invention, is disclosed method of treating a disease in a mammal wherein the disease is capable of being, modulated by PPARdelta ligand

binding activity, which comprises administering to said mammal having said disease a therapeutically effective amount of a compound of formula I.

In a further aspect of this embodiment, is disclosed a method wherein said disease is a demyelinating disease selected from the group consisting of multiple sclerosis, Charcot-Marie-Tooth disease, Pelizaeus-Merzbacher disease, encephalomyelitis, neuromyelitis optica, adrenoleukodystrophy, Guillian-Barre syndrome and disorders in which myelin forming glial cells are damaged including spinal cord injuries, neuropathies and nerve injury.

In another aspect of this embodiment, is disclosed a method wherein the demyelinating disease is multiple sclerosis.

In still another aspect of this invention is disclosed a method wherein said disease is selected from the group consisting of obesity, hypertriglyceridemia, hyperlipidemia, hypoalphalipoproteinemia, hypercholesterolemia, dyslipidemia, Syndrome X, Type II diabetes mellitus and complications thereof selected from the group consisting of neuropathy, nephropathy, retinopathy and cataracts, hyperinsulinemia, impaired glucose tolerance, insulin resistance, atherosclerosis, hypertension, coronary heart disease, peripheral vascular disease or congestive heart failure.

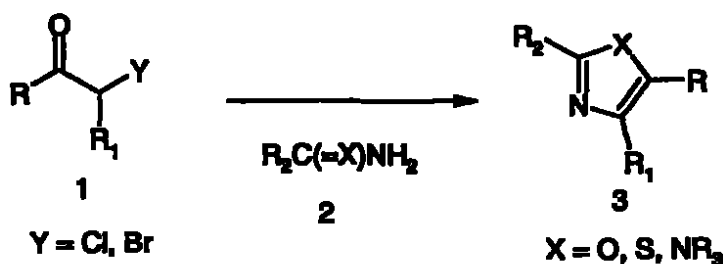
The compounds disclosed herein can be synthesized according to the following procedures of Schemes, wherein the X, and R substituents are as identified for formula (I), above unless otherwise noted. It being understood that certain starting materials in the synthetic schemes would be commercially available or whose synthesis would be obvious to those skilled in the art.

If necessary, in the following synthetic schemes, reactive functional groups present in the compounds described in this invention may be protected by suitable protecting groups. The protecting group may be removed at a later stage of the synthesis. Procedures for protecting reactive functional groups and their subsequent removal may be found in T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley and Sons, 1991.

Scheme A shows the synthesis of the appropriate imidazole, oxazole or thiazole, intermediates for compounds of formula I wherein X is O, S, NR₃. The heterocycles can be prepared using methods known in the chemical literature (for reviews see Katritzky, A.R.; Rees, C.W. Eds. *Comprehensive Heterocyclic Chemistry*, Vol. 5; Pergamon Press (1984); Katritzky, A.R.; Rees, C.W.; Scriven, E.F.V. Eds. *Comprehensive Heterocyclic Chemistry II*; Vols 3 & 4, Pergamon Press (1996)). Specifically, said oxazoles, imidazoles and thiazoles can be prepared by fusion of an appropriate α halo-ketone 1, respectively, with an amide,

amidine or a thioamide (general formula 2), at temperatures ranging from about 40 °C to 150 °C to give the intermediate heterocycles 3.

Scheme A



In Scheme B the general synthesis of compounds of formula I wherein Z is $-\text{O}(\text{CH}_2)_n-$ is shown. Accordingly, in Step B1 the appropriately substituted carboxylic acid ester 4, which can be synthesized as illustrated in Scheme A is reduced to the alcohol 5 by methods that are well known in the art. For example, the reduction may be effected by aluminum hydrides such as lithium aluminum hydrides or diisobutylaluminum hydride in an inert solvent. In Step B2, the alcohol functional group in compound 5, is converted to a leaving group to give compound 6, wherein Lg is a leaving group such as halogen, or sulfonate esters, for example mesylates or tosylates. Conversion to the leaving group can be accomplished by reaction of the alcohol with reagents such N-bromosuccinimide in the presence of triphenylphosphine to produce a compound wherein the leaving group is bromide, or reaction with thionyl chloride to give a compound wherein the leaving group is chloride. If a sulfonate ester is desired, reaction of compound 5 with an appropriate sulfonyl chloride in the presence of a suitable base would produce the desired sulfonate ester. For example, reaction of compound 5 with methanesulfonyl chloride in the presence of an organic base such as triethylamine or pyridine in an inert solvent would give compound 6 wherein the leaving group is OSO_2CH_3 .

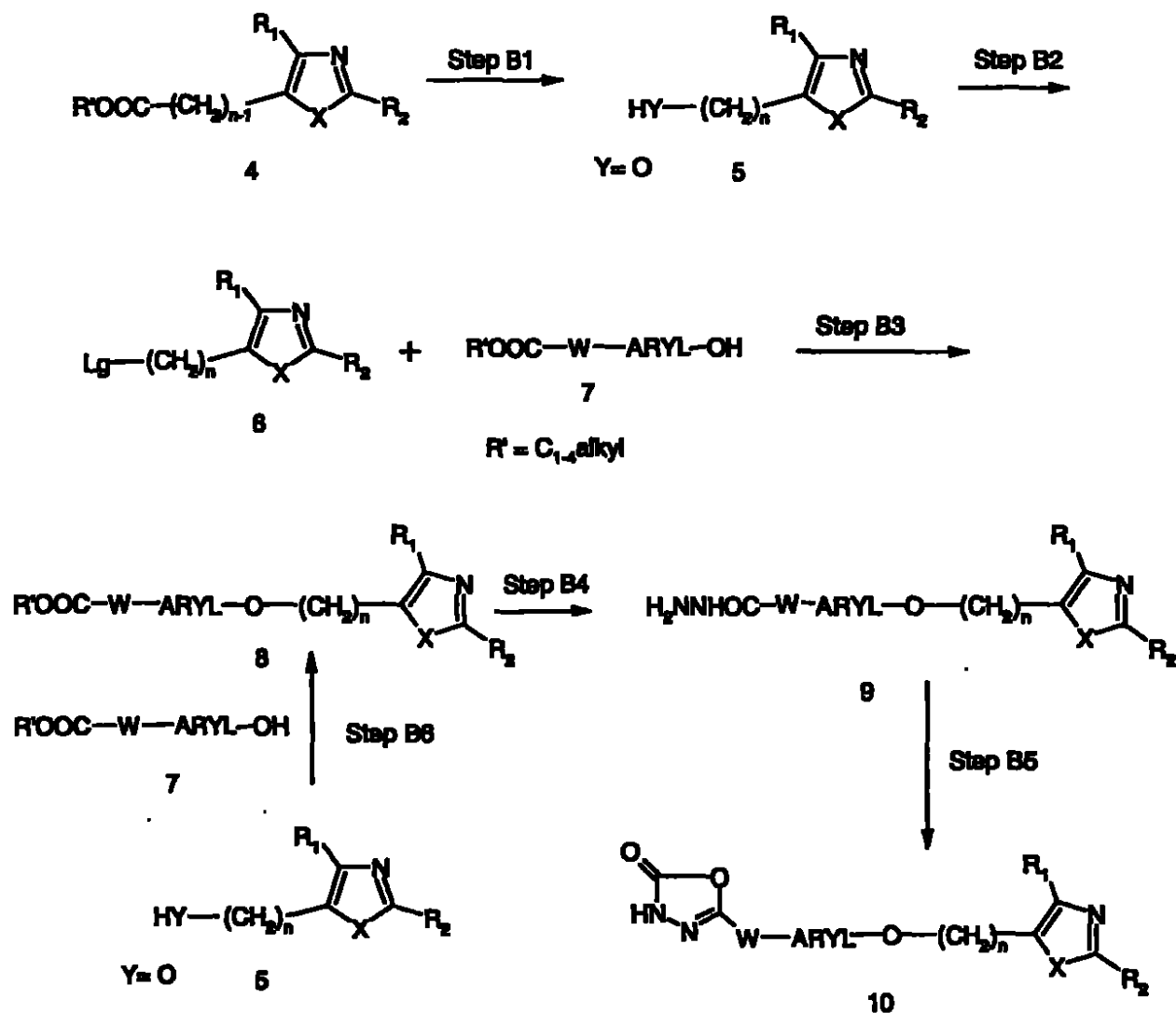
In Step B3 an appropriately substituted hydroxy aryl ester, 7 is reacted with the heterocycle, 6 to displace the leaving group to afford coupled ester, 8. The displacement reaction is run under conditions well known in the art. Typically the reaction is run in the presence of a base such as sodium hydride or other inorganic bases such as alkali carbonates or alkali hydroxides in an inert solvent. The temperature of the reaction, although not critical, is from 0°C to the reflux temperature of the inert solvent.

Compound 8, in Step B4 is then treated with hydrazine either neat or in a suitable organic solvent at elevated temperatures to give the acid hydrazide, 9. Typically the reaction is run at a temperature of between 50°C and the reflux temperature of the organic solvent.

Cyclization of the acid hydrazide 9, in Step B5, to the target 1,3,4-oxadiazol-2-ones, 10 is accomplished by treatment of compound 9 with a chloroformate in the presence of an organic base such as pyridine followed by treatment with strong, hindered amine base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in a suitable organic solvent such as acetonitrile in a sealed tube at elevated temperature. Typically, the reaction can be run from 100°C to 200°C. The 1,3,4-oxadiazol-2-ones may also be synthesized by reacting compound 9 with phosgene. See Stempel, A., et al., *J. Org. Chem.* 1955, 20, 412.

In Step B6, an alternative synthesis of the coupled ester, 8 is illustrated. Accordingly, the alcohol, 5 can be reacted with the hydroxyaryl ester, 8 in the presence of a triaryl or trialkylphosphine, such as triphenylphosphine or tri- *n*-butylphosphine and diethylazodicarboxylate in an inert solvent, for example THF or dichloromethane to afford the coupled ester 8. Typically the reaction is run at a temperature between room temperature and the reflux temperature of the inert solvent.

Scheme B



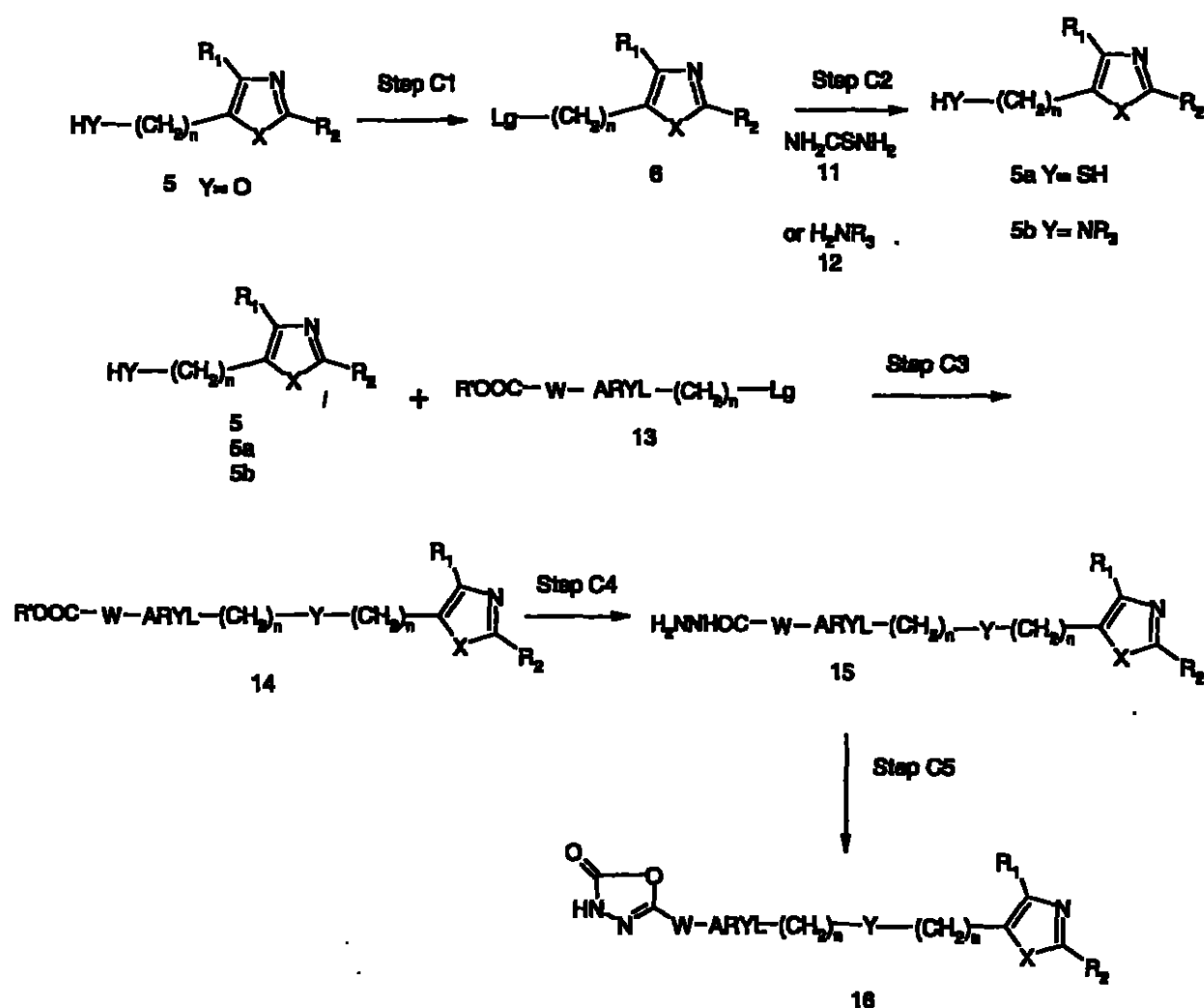
Scheme C illustrates the synthesis of the compound of formula I wherein Z is $-(\text{CH}_2)_n-$ Y- $(\text{CH}_2)_n-$. The scheme is most useful to synthesize compounds wherein n represents 1 or 2 in the alkylene chain attached to ARYL. In Step C1 compound 5 (Y= O) is converted to compound 6 (wherein Lg is chloro or bromo) as described in Scheme B, Step B2. Compound 6 is then reacted with thiourea, compound 11, under conditions similar to those found in Treau, M. et al. *Heterocycles*, 2001, 55 (9), 1727-1735, to produce the thiol, 5a.

When compound 6 is reacted with a primary amine 12, the aminoalkyl heterocycle 5b is produced. This displacement of a leaving group by an amine is well known to those skilled in the art. Typically, the displacement reaction is run in a polar organic solvent in the presence of an organic base that acts as an acid scavenger. Although not critical, the displacement reaction is run at a temperature of between ambient to reflux temperature of the solvent.

In Step C3 compounds 5, 5a and 5b can be reacted with compound 13 to afford the coupled arylester, 14, wherein Y is O, S or NR₃. Thus, when compounds 5 (Y= O) and 5a (Y= S) are reacted with 13 to displace the leaving group, the reaction will typically be run in the presence of a strong base, for example sodium hydride, in a polar aprotic solvent, such as DMF or DMSO at temperatures of about between 0°C to 150°C. When compound 5b (Y= NR₃) is reacted with 14, conditions identical to those described above in Step C2 for the primary amine are used.

Synthesis of the desired 1,3,4-oxadiazol-2-ones 16, from compound 14 is accomplished in the two steps (C4 and C5) exactly as described in Scheme B, Steps B4 and B5.

Scheme C



In Scheme D an alternative approach to compounds of formula I wherein Z is -(CH₂)_n-Y-(CH₂)_n- is shown. The scheme is most useful to synthesize compounds wherein n is 3 to 5 in the alkylene chain attached to ARYL.

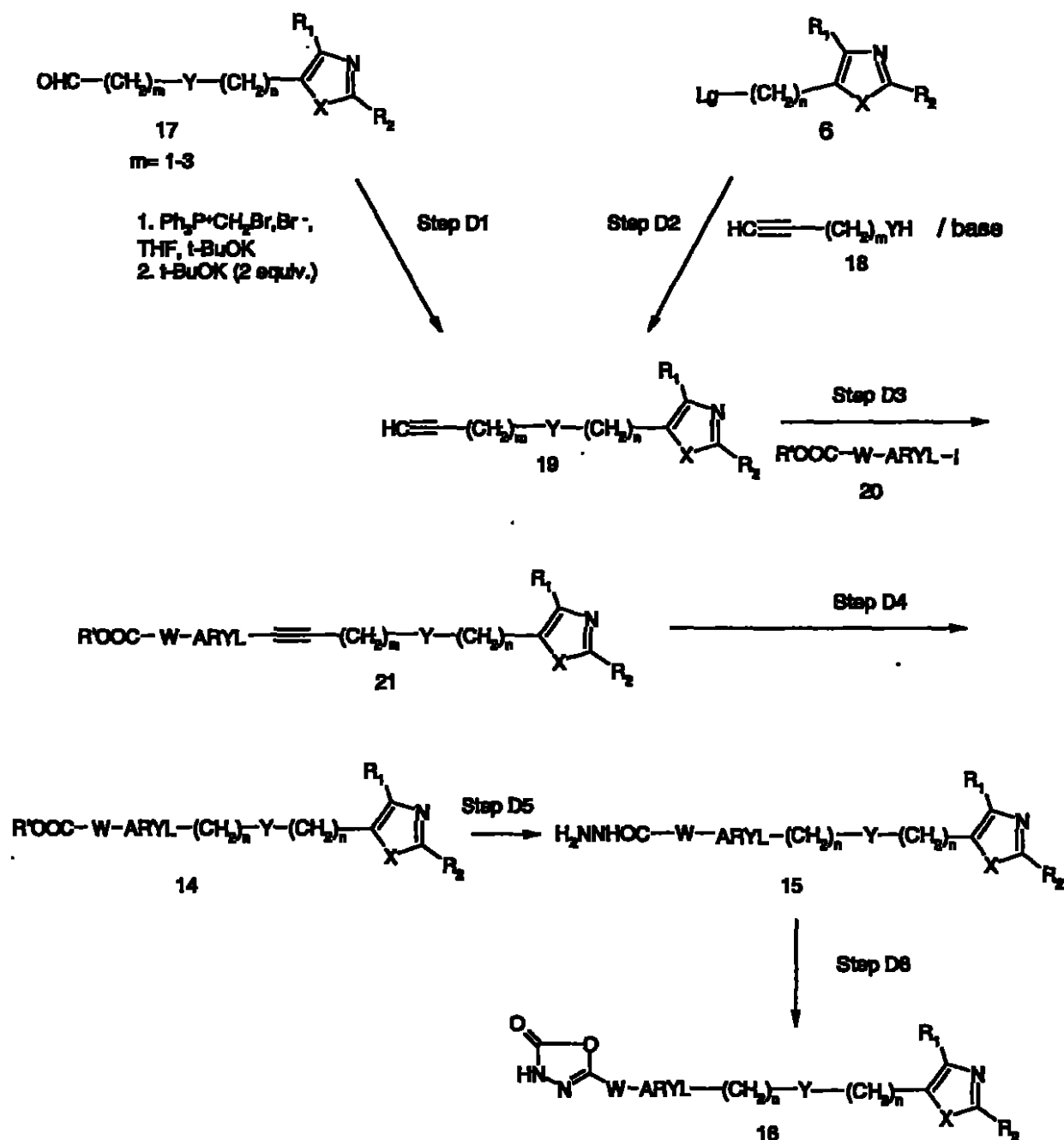
In Step D1 the terminal aldehyde compound 17, which can be synthesized by the method described in Scheme A, is converted in a two-step reaction sequence to the terminal acetylene, 19. Thus, reaction of 17 with bromomethylenetriphenylphosphorane (first step) with potassium t-BuOK produces an intermediate bromoolefin (not shown), which is subsequently treated with 2 equivalents of t-BuOK (second step) to form the acetylene, 19. The reaction sequence for the conversion is described in Pianetti, P., *Tet. Letters*, 1986, 48, 5853-5856. Also, see Corey, E. J., et al. *J. Am. Chem. Soc.*, 1969, 91, 4318-4320.

Alternatively, as shown in Step D2 intermediates of the type 19 can be prepared by displacement of a leaving group from an intermediate such as 6 (see Scheme C) using a nucleophile, such as 18, wherein a terminal acetylene is incorporated.

In Step D3, Sonogashira coupling of acetylenic intermediate, 19 with the aryl iodide, 20 is effected in the presence of tetrakis(triphenylphosphine)palladium (0), cuprous iodide and a suitable organic base in an inert solvent to yield the coupled terminal acetylene 21. The reduction of the acetylene, 21 can then be accomplished in Step D4 by catalytic hydrogenation of compound 21 to give the saturated ester 14. Typically, the reduction can be effected by use of catalysts such as palladium on carbon or chlorotris(triphenylphosphine)rhodium(I) in an inert organic solvent with hydrogen at pressures between 30 to 300 p.s.i.. The reduction can be run at a temperature between room temperature and 175°C.

Synthesis of the desired 1,3,4-oxadiazol-2-ones 16, from compound 14 is accomplished in two steps (D5 and D6) exactly as described in Scheme B, Steps B4 and B5.

Scheme D

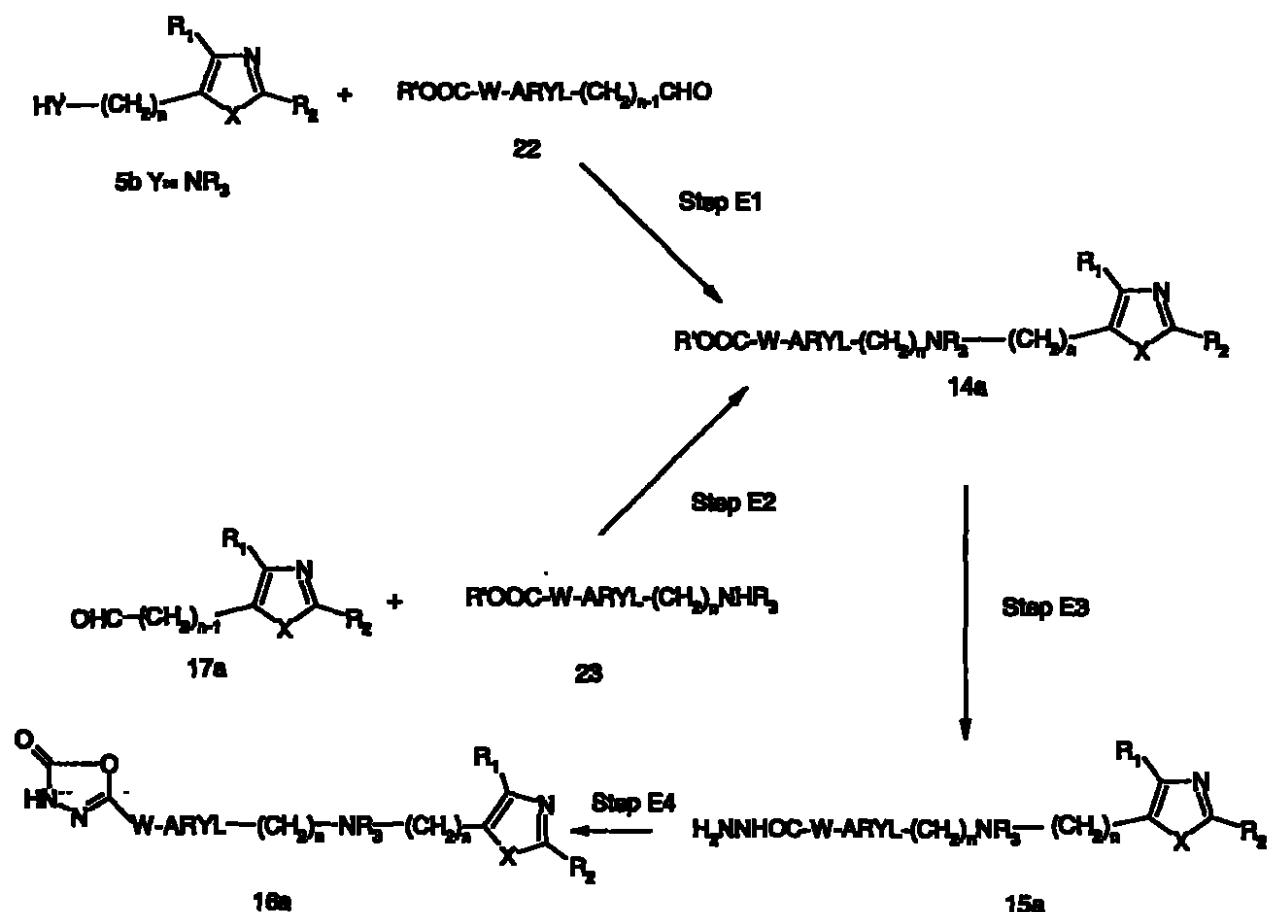


Scheme E illustrates a particular synthesis of compounds of formula I wherein Z is -
 5 $(\text{CH}_2)_n\text{NR}_3(\text{CH}_2)_n-$. In this approach, the linker Z is constructed by a reductive amination of an
 aldehyde with an amine. For example, in Step E1 treatment of 5b (wherein $\text{Y} = \text{NR}_3$) with an
 aldehyde, such as 4-formyl-benzoic acid methyl ester ($n=1$), compound 22, in a polar solvent,
 usually an alcohol or an alcohol THF mixture, followed by treatment with a reducing agent
 such as sodium triacetoxy-borohydride provides the required intermediate 14a ($n=1$).

Similarly in Step E2, treatment of an aldehyde such as 17a as with an amine, such as 4-aminoalkyl benzoic acid methyl ester ($n=1$), compound 23, provides 14a, wherein n is 1 and R_3 is H for $-(CH_2)_nNR_3$. Compound 14a in steps E3 and E4 is converted to 1,3,4-oxadiazol-2-ones 16a as described in Scheme B, Steps B4 and B5.

- 5 More generally, appropriate amines ($R'OOC-ARYL-(CH_2)_nNHR_3$) are prepared from the corresponding nitriles or nitro compounds by catalytic hydrogenation or from acetylenic amines and an aryl iodide or bromide by Sonogashira coupling followed by catalytic hydrogenation as described in Scheme D.

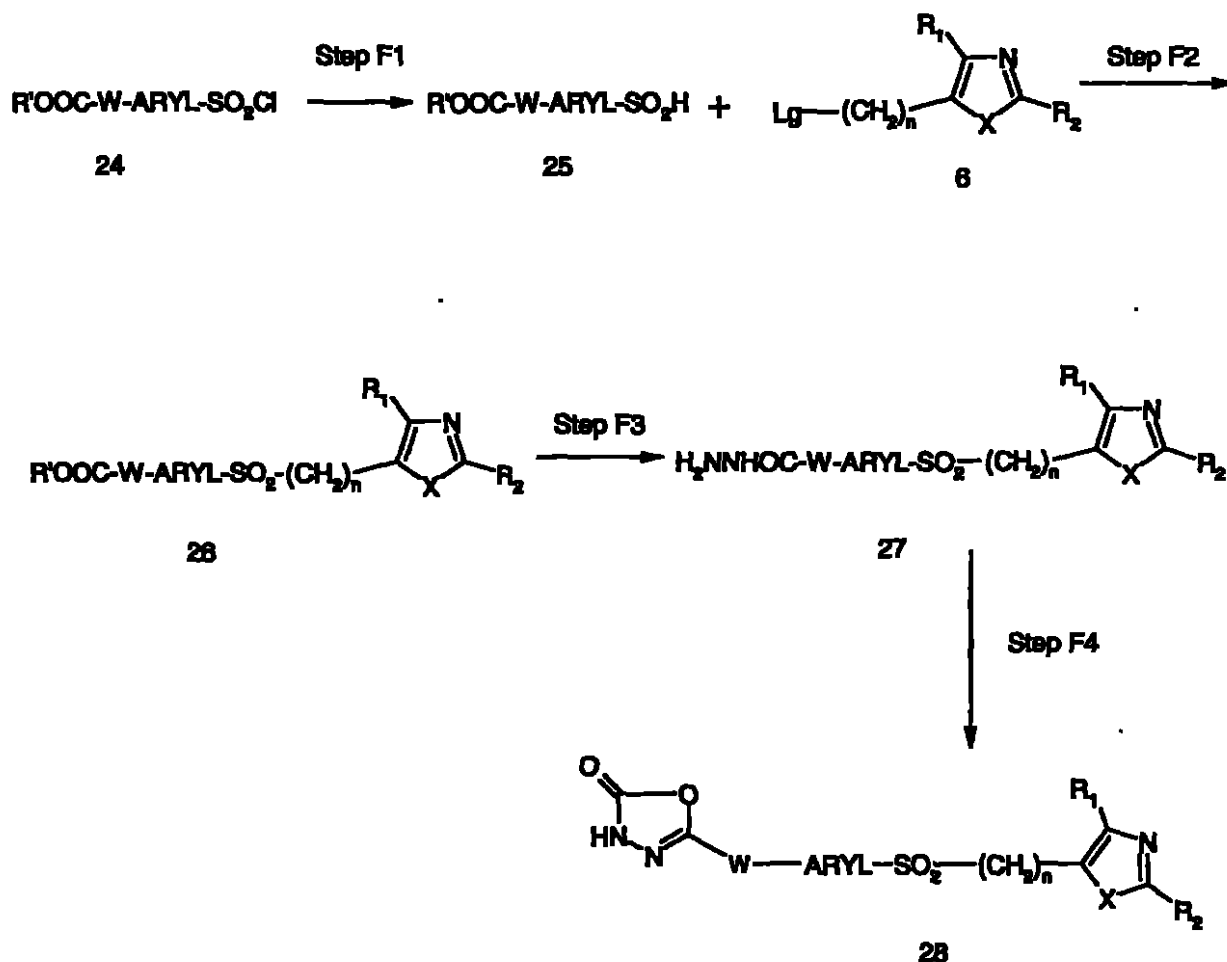
Scheme E



15 Scheme F illustrates the synthesis of compounds of formula I wherein Z is $-SO_2$ $(CH_2)_n-$. In Step F1 treatment of an aryl sulfonyl chloride, 24 with aqueous sodium sulfite provides the sulfinic acid, 25. Reaction of 25, as in Step F2, with an intermediate such as 6 in a polar solvent such as DMF, acetonitrile or ethanol in the presence of a base such as DBU, pyridine, sodium methoxide or sodium hydroxide provides intermediate 26. Intermediate 26

is converted to the corresponding 1,3,4-oxadiazol-2-one, 28 in Steps F3 and F4 as illustrated in Scheme B, Steps B4 and B5.

Scheme F



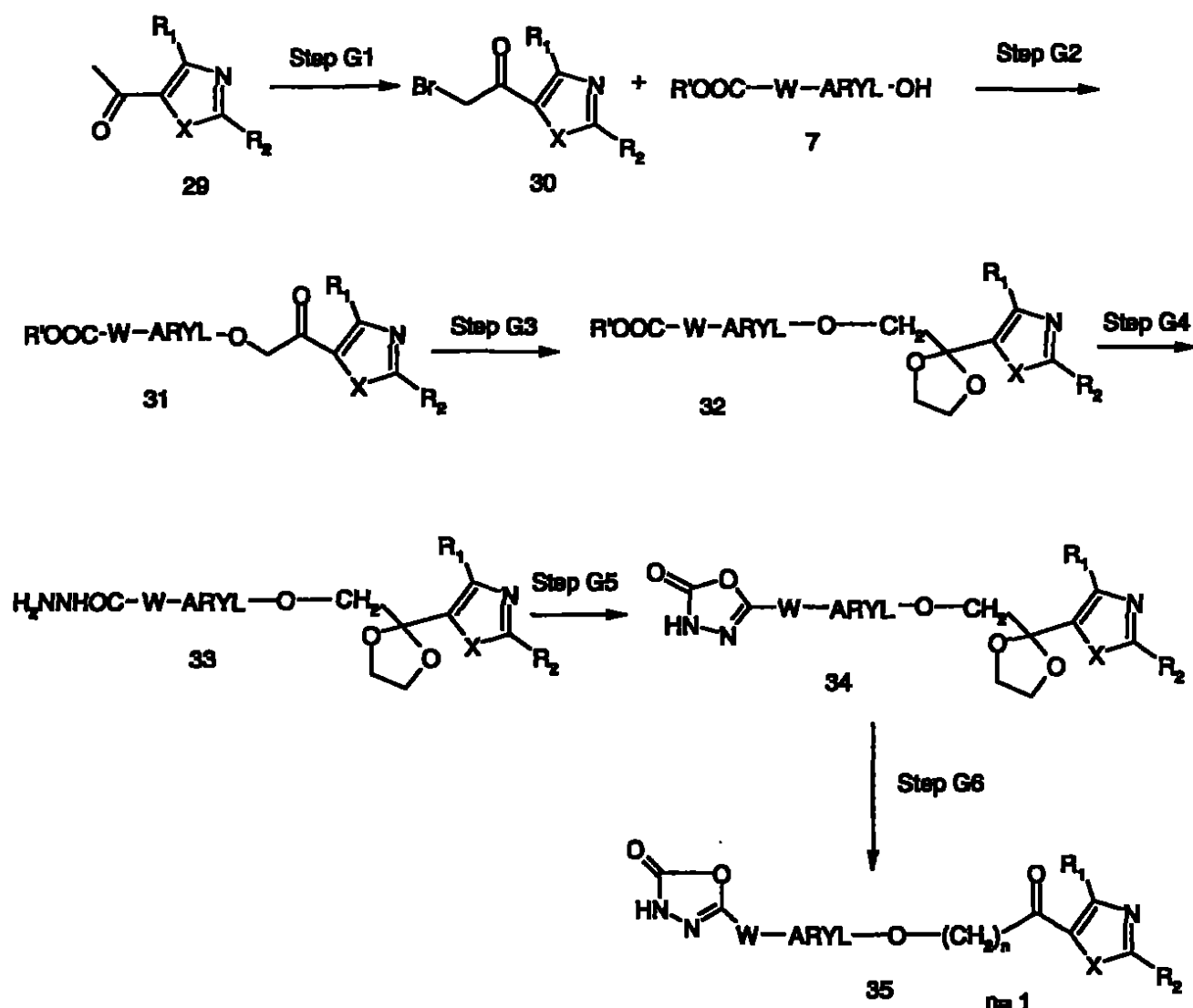
Scheme G illustrates the synthesis of compound of formula I wherein Z is—

$\text{O}(\text{CH}_2)_n\text{CO}-$. The scheme illustrates the case wherein n is 1. The starting 2-acyl heterocycle, 29 can be synthesized from the corresponding carboxylic acid (prepared by the method illustrated in Scheme A) by addition of an appropriate Grignard reagent to an intermediate N-methoxy N-methyl carboxamide (Khlestkin, V.K. et al.; Current Organic Chemistry, 2003, 7(10), 967-993. and Singh, J. et al., Journal für Praktische Chemie, 2000, 342, 340-347). Preparation of the intermediate N-methoxy-N-methyl carboxamide is most conveniently carried out by reaction of the acid with N-methoxy-N-methyl hydroxylamine hydrochloride in the presence of a peptide coupling reagent such as EDC, DCC, DMPU and a tertiary amine base such as diisopropylethylamine or triethylamine.

Thus in hand, 29 is brominated to produce the bromoketone 30, as shown in Step G1. The bromination can be accomplished by well-known methods, for example reaction of 29 with pyridinium bromide per bromide in acetic acid or reaction of 29 with Br₂ in an inert organic solvent such as dichloromethane. The resulting bromoketone 30, in Step G2, is
5 reacted with the arylhydroxy ester 7 under conditions described in Scheme B (Step B3) to afford the coupled ester 31. The ketone functionality in 31 is protected as a ketal 32, as shown in Step G3 by methods well known in the art. Compound 32 is then converted to the 1,3,4-oxadizol-2-one ketal 34, in Steps G4 to G5 by the standard sequence as described in Scheme B (B4 and B5). Finally, in Step G6, the ketal functionality in 34 is cleaved, for example, with
10 mineral acid in THF-methanol-water or other methods known in the art to afford the target structure 35.

It would be evident to one skilled in the art that the above procedure of Scheme G could be used to synthesize analogs where n is 2-5 for compound 35 by starting with a bromoketone, compound 30, with a larger bromoalkanoyl substituent (Br(CH₂)_nCO-, wherein
15 n is 2 to 5).

Scheme G

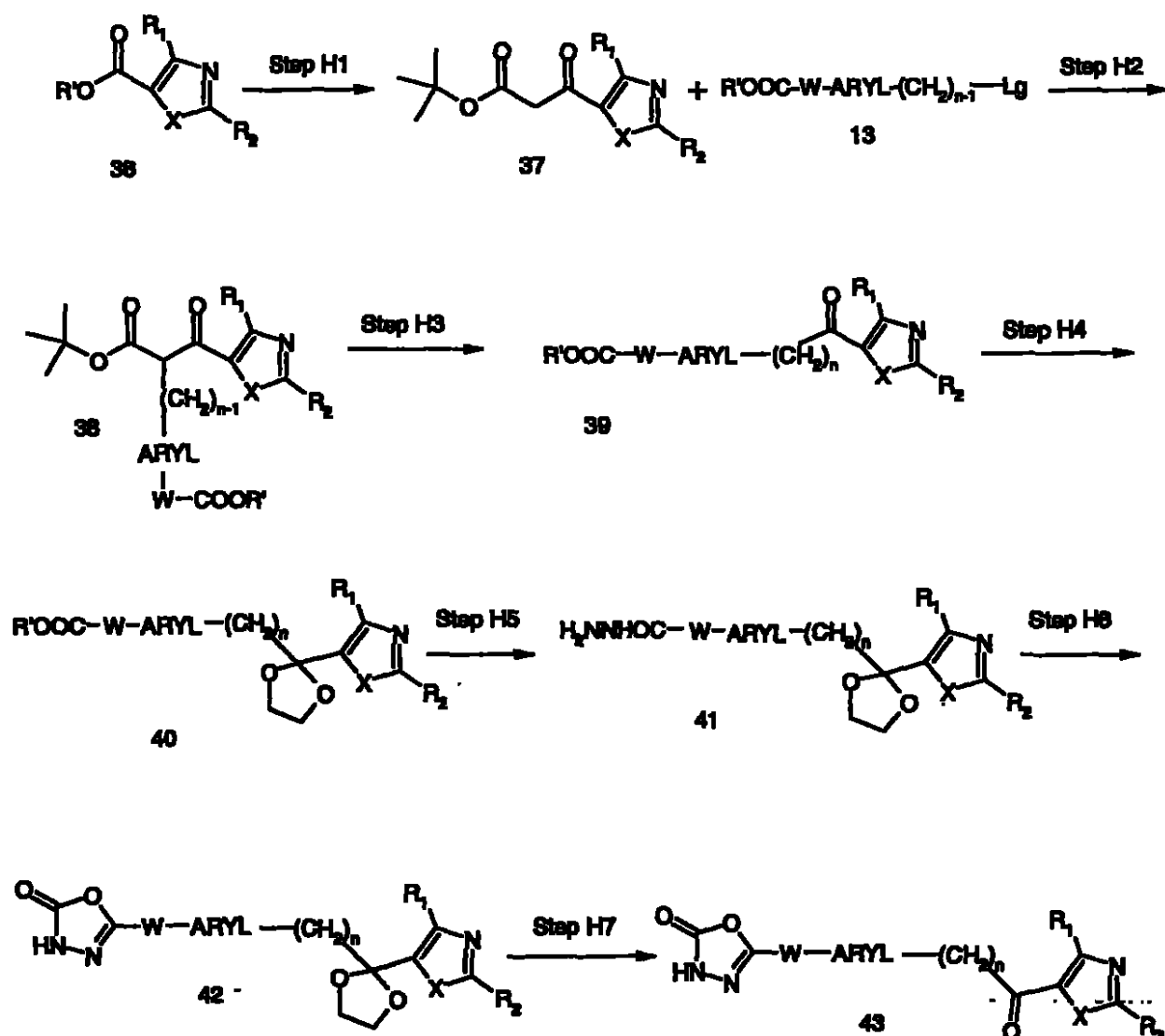


Scheme H illustrates the procedure for the preparation of compounds of formula I wherein Z is $-(CH_2)_nCO-$. In Step H1, the appropriate methoxycarbonyl-substituted heterocycle, 36 is treated with 2 equivalents of the lithium enolate of t-butylacetate in a solvent such as THF or DME at a temperature ranging from -78°C to room temperature to provide the ketoacetate intermediate 37. In Step H2, treatment of 37 with a base such as sodium hydride in an inert solvent at a temperature between -10°C and room temperature followed by alkylation of the resulting anion with an electrophile such as 13 yields the advanced intermediate ketodiester 38. The decarboxylation shown in Step H3 and can be accomplished by first treatment of 38 with TFA in an inert solvent such as dichloromethane followed by thermolysis at a temperature between 70°C and 150°C to provide intermediate ketoester 39. The ketone functionality in 39 is protected as a ketal 40, as shown in Step H4 by methods well known in the art. Compound 40 is then converted to the 1,3,4-oxadiazol-2-one

ketal 42 in Steps H5 to H6 by the standard sequence as described in Scheme B (B4 and B5). Finally, in Step H7, the ketal functionality in 42 is cleaved, as described above in Scheme G, Step G6 to afford the desired 1,3,4-oxadiazol-2-one, compound 43.

5

Scheme H



Biological Examples:

The following test protocols are used to ascertain the biological properties of the compounds of this invention. The following examples are being presented to further illustrate the invention. However, they should not be construed as limiting the invention in any manner.

10

Determination of EC₅₀ values in the cell based PPARdelta-GAL4 assay:

Principle

The potency of substances, which bind to human PPAR delta and activate it in an agonistic manner, is analyzed using a stably transfected HEK cell line (HEK= human embryo kidney) which is referred to here as PPAR delta reporter cell line. The PPAR delta reporter cell line contains two genetic elements, a luciferase reporter element (pdeltaM-GAL4-Luc-Zeo) and a PPAR delta fusion protein (GR-GAL4-humanPPAR delta-LBD), which mediates expression of the luciferase reporter element depending on a PPAR delta ligand. The stably and constitutively expressed fusion protein GR-GAL4-humanPPAR delta-LBD binds in the cell nucleus of the PPAR delta reporter cell line via the GAL4 protein portion to the GAL4 DNA binding motifs 5'-upstream of the luciferase reporter element which is stably integrated in the genome of the cell line. There is only little expression of the luciferase reporter gene in the absence of a PPAR delta ligand if fatty acid-depleted fetal calf serum (cs-FCS) is used in the assay. PPAR delta ligands bind and activate the PPAR delta fusion protein and thereby stimulate expression of the luciferase reporter gene. The luciferase, which is formed can be detected by means of chemiluminescence via an appropriate substrate.

Construction of the PPAR delta reporter cell line:

The production of the stable PPAR delta reporter cell line is based on a stable HEK-cell clone which was stably transfected with a luciferase reporter element. This step was already described above in the section "construction of the PPAR alpha reporter cell line". In a second step, the PPAR delta fusion protein (GR-GAL4-humanPPAR delta-LBD) was stably introduced into this cell clone. For this purpose, the cDNA coding for the N-terminal 76 amino acids of the glucocorticoid receptor (Accession # P04150) was linked to the cDNA section coding for amino acids 1-147 of the yeast transcription factor GAL4 (Accession # P04386). The cDNA of the ligand-binding domain of the human PPAR delta receptor (amino acids S139-Y441; Accession # L07592) was cloned in at the 3'-end of this GR-GAL4 construct. The fusion construct prepared in this way (GR-GAL4-humanPPAR delta-LBD) was recloned into the plasmid pcDNA3 (Invitrogen) in order to enable constitutive expression by the cytomegalovirus promoter. This plasmid was linearized with a restriction endonuclease and stably transfected into the previously described cell clone containing the luciferase

reporter element. The resulting PPAR delta reporter cell line which contains a luciferase reporter element and constitutively expresses the PPAR delta fusion protein (GR-GAL4-human PPAR delta-LBD) was isolated by selection with zeocin (0.5 mg/ml) and G418 (0.5 mg/ml).

5

Assay procedure and evaluation:

The activity of PPAR delta agonists is determined in a 3-day assay, which is described below:

10 Day 1

The PPAR delta reporter cell line is cultivated to 80% confluence in DMEM (# 41965-039, Invitrogen) which is mixed with the following additions: 10% cs-FCS (fetal calf serum; #SH-30068.03, Hyclone), 0.5 mg/ml zeocin (#R250-01, Invitrogen), 0.5 mg/ml G418 (#10131-027, Invitrogen), 1% penicillin-streptomycin solution (#15140-122, Invitrogen) and 2 mM L-glutamine (#25030-024, Invitrogen). The cultivation takes place in standard cell culture bottles (# 353112, Becton Dickinson) in a cell culture incubator at 37°C in the presence of 5% CO₂. The 80%-confluent cells are washed once with 15 ml of PBS (#14190-094, Invitrogen), treated with 3 ml of trypsin solution (#25300-054, Invitrogen) at 37°C for 2 min, taken up in 5 ml of the DMEM described and counted in a cell counter. After dilution to 500.000 cells/ml, 35,000 cells are seeded in each well in a volume of 180 µL of a 96 well microtiter plate with a clear plastic base (#3610, Corning Costar). The plates are incubated in the cell culture incubator at 37°C and 5% CO₂ for 24 h.

Day 2

25 PPAR delta agonists to be tested are dissolved in DMSO in a concentration of 10 mM. This stock solution is diluted in DMEM (#41965-039, Invitrogen) which is mixed with 5% cs-FCS (#SH-30068.03, Hyclone), 2 mM L-glutamine (#25030-024, Invitrogen) and the previously described antibiotics (zeocin, G418, penicillin and streptomycin). Test substances are tested in 11 different concentrations in the range from 10 µM to 100 pM. More potent compounds are tested in concentration ranges from 1 µM to 10 pM or between 100 nM and 1 pM.

30

The medium of the PPAR delta reporter cell line seeded on day 1 is completely is either completely removed by aspiration or not, and the test substances diluted in medium are

immediately added to the cells. The dilution and addition of the substances is carried out by a robot (Beckman FX). The final volume of the test substances diluted in medium is 100 μ l per well of a 96 well microtiter plate. The DMSO concentration in the assay is less than 0.1 % v/v in order to avoid cytotoxic effects of the solvent.

5 Each plate was charged with a standard PPAR delta agonist, which was likewise diluted in 11 different concentrations, in order to demonstrate the functioning of the assay in each individual plate. The assay plates are incubated in an incubator at 37°C and 5% CO₂ for 24 h.

Alternatively, 20 μ L of a 10x final concentration of the test substance is added directly to the 180 μ L containing the plated cells. The test substances are tested in 8 different
10 concentrations, in triplicate, in this assay plate set-up.

Day 3

The PPAR delta reporter cells treated with the test substances are removed from the incubator, and the medium is aspirated off. The cells are lysed by pipetting 50 μ l of Bright
15 Glo reagent (from Promega) into each well of a 96 well microtiter plate. After incubation at room temperature in the dark for 10 minutes, the microtiter plates are measured in the luminometer (Trilux from Wallac). The measuring time for each well of a microtiter plate is 1 sec.

20 Evaluation:

The raw data from the luminometer are transferred into a Microsoft Excel file. Dose-effect plots and EC₅₀ values of PPAR agonists are calculated using the XLFit program as specified by the manufacturer (IDBS).

25 PPARdelta EC₅₀ values in the range of 1nM to >10 μ M were measured for the PPAR modulators of the examples in this application. Compounds of the invention of formula I can act as agonists or antagonists. The assay to determine partial agonist or antagonist activity is described below.

Determination of Effectiveness of Partial Agonists or Antagonists At the PPARdelta Receptor

This assay determines if compounds act as partial agonists or antagonists at the PPARdelta receptor.

5 The plating and harvesting of the assay plates is as described in Day 1 and 3 above.

Day 2

 The partial agonist or antagonist and a known selective agonist are diluted in DMEM (#41965-039, Invitrogen), which is mixed with 10% cs-FCS (#SH-30068.03, Hyclone), 2 mM L-glutamine (#25030-024, Invitrogen) and the previously described antibiotics (zeocin, G418, penicillin and streptomycin) to 20X desired final concentrations. Ten microliters of the partial agonist or antagonist is added to the cell-containing assay plate. The assay plates are incubated in an incubator at 37°C and 5% CO₂ for 30 minutes. Ten microliters of the 20X known selective agonists are then added, after the partial agonist or antagonist pre-incubation. The assay plates are incubated in an incubator at 37°C and 5% CO₂ for 24 h. The effect on the known selective agonists EC₅₀'s is determined for each partial agonist or antagonist concentration.

10
15

SPA PPAR delta-LBD Binding Assay

20 **Stock Solutions:**

 1 M Tris (pH=8.0 or pH=7.6)(Gene Medicine Stock Room)

 2 M KCl (Powder in N2140)

 Tween 20

25 100 mM DTT

 13.9 µM GW2331 in EtOH HOT

 10 mM GW 2331 in DMSO COLD

30 PPAR-alpha (Conc. varies)

 Ex: .884 µg/µl

Wash Buffer: (Store at 4°C. Buffer is good for one week)

- 10 mM Tris(pH=7.6 or 8) 10 ml
- 50 mM KCl 25 ml
- 0.05 % Tween 20 0.5 ml
- 5 Millipore Water 964.5
- Check PH=7.6

Binding Buffer:(Prepare fresh binding buffer every time)

- 10 Wash Buffer 50 ml
- 10 mM DTT 5.5ml

Preparation of Reaction Reagents for 1 Plate:

15 **Glutathione Coated SPA beads**

Each SPA bead bottle contains 500 mg beads
Reconstitute 500mg of SPA beads in 5 ml of wash buffer, and will be good for few weeks
Store at 4°C

20 **Prepare diluted SPA beads in the binding buffer.**

Adding 1 ml of above reconstituted SPA beads to 60 ml of Binding buffer
adding 20 µl of above diluted beads to each well of a 96-well plate.

25 **Use 2ml of above diluted beads for each plate (no dead volume included).**

3H GW-2331 plus GST-PPAR delta-LBD (for one 96-well plate no dead volume) 13.9 µM
40nM / well

30 **3.0 ml/plate (Including dead volume)**
If 3H-GW2331 specific activity is 1mci/ml(From Amersham), dilute 17 µl of 3H GW-2331
into 3.0 ml of Binding Buffer = .08 µM

If protein concentration is 1mg/mL, add 21 µl of proteins into 3.0 ml of binding buffer.

In Summary: ONE 96-well plate: 3000 µL Binding Buffer + 17 µL of 3H-GW2331+21 µL of

5 GST-PPAR-delta(1mg/ml)

Control Plates

A 96-well Mother Plate(For 2 control Plates)

10

In column #1:

Add 5 µl of cold GW2331(10 mM) to the wells E-H

Add 45 µL of DMSO to the wells A-H

15 In column #12 (3-fold dilution):

Add 10 µL of cold GW2331(10 mM) to the well A.

then add 90 µl of DMSO to the well A, mix well the solution.

add 20 µl of DMSO to the wells B-H

take 10 µl solution from the well A to B, mix well,

20 then take 10 µl solution from B to C, mix well,

then take 10 µl solution from C to D, mix well.

.....

Finally, take 10 µl from F to H.

25 A control Plate (for 8 Reaction Plates)

A control plate is 1:10 dilution of the mother plate. The dilution buffer is the wash buffer.

Sample plates

30

To fresh CPC library plate, add 90 µl of DMSO

Take 10 µl of DMSO dilution and add it to 90 µl of wash buffer in a sample plate

Reaction Plates:

5 Add 20 µl of SPA beads and 30 µl of 3H-GW2331 with GST-PPAR-delta to each well of a Reaction Plate.

Add 5 µl compounds from each well of the sample plate into columns 2 to 11 of a reaction plate.

10 Add 5 µl compounds from column 1 and column 12 of the control plate to the column 1 and column 12 of the reaction plate.

96-well SPA Protocol:

15 Let reaction plates equilibrate for 20 minutes to 2 hours.

Seal the plates before counting in a Microbeta counter (Wallac).

Calculate IC₅₀.

20 In the SPA PPAR delta-LBD Binding Assay IC₅₀ values in the range of 1 nM to >10 µM were measured for the PPAR modulators of the examples in this application. Compounds of the invention of formula I can act as agonists or antagonists.

25 **RAT/MICE Oligodendrocyte cultures**

Preparation of cells:

1. Primary rat oligodendrocyte progenitor cells are obtained from the neocortex of newborn (postnatal days 2-3) rats or mice and are enriched, after removal of microglia, by mechanical separation from the astrocytic monolayer using a modification of the technique originally described by McCarthy and de Vellis (1980).
2. Remove the meninges from neonatal rat brain and mechanically dissociate tissue. Plate cells on T75 flasks and feed cells with DMEM/F12 + 10% FBS.

3. Collect oligodendrocytes growing on the astrocyte bed layer by shaking-off method fourteen days after the original prep date. Centrifuge the suspension and resuspend the cell pellet in serum free media (SFM; DMEM combined with 25 μ g/ml transferrin, 30 nM triiodothyronine, 20 nM hydrocortisone, 20 nM progesterone, 10 nM biotin, 1x trace elements, 30 nM selenium, 1 μ g/ml putrescine, 0.1% BSA, 5 U/ml PenStrep, 10 μ g/ml insulin) supplemented with the following growth factors: Platelet derived growth factor-AA (PDGF) and fibroblast growth factor-2 (FGF).
4. Plate the cells on PDL-coated dishes and incubate at 37°C with 6-7% CO₂.
5. Media components are replaced every 48 hr to keep the cells in a progenitor state.

Progenitor cell passaging to increase cell numbers for screening assays:

1. When the culture are confluent, rinse the culture with PBS, add trypsin and incubate for ~2-3 min at 37°C.
2. Neutralize and centrifuge the cell suspension at 900g for 5 min.
3. Resuspend the cell pellet in SFM + PDGF/FGF.
4. Feed the cells with fresh growth factors every 48 hrs to keep enrich for rapidly dividing progenitor cells.
5. Cells are passaged no more than 4-5 times prior to experimental assays.
6. All experiments involving oligodendrocyte progenitor cells were done using cells that were continuously maintained under these conditions. Greater than 95% of all cells were A2B5 immunopositive and expressed 2' 3' -cyclic nucleotide 3' -phosphodiesterase II mRNA.
7. To generate mature oligodendrocytes, 24 h after plating progenitor cells were switched to SFM supplemented with or without IGF-I and grown under these conditions for 7 d prior to experimental assays.
8. Alternatively, the enriched rat Central Glia-4 (CG4) progenitor cell line may be used, which is maintained in base media (DMEM, with 2 mM glutamine, 1mM sodium pyruvate, biotin (40 nM), insulin (1 μ M) and N1) supplemented with 30% conditioned media from the B-104 neuroblastoma cell line. To induce differentiation, CG4 cells are switched to base media with 1% fetal calf serum (removed after 2 days) and insulin (500 nM). A2B5 and MBP immunoreactivity is used to confirm >95% enrichment in immature and mature cultures, respectively.

Rat/Mouse Culture Compound Treatment:

1. Put 10,000 – 15,000 cells /well in 24-well PDL coated plates and culture the cells in presence of mitogen (10 ng/ml) overnight.
2. In the presence of mitogen:
 - 5 a. Next day, remove the old medium and add compounds in fresh medium (with mitogen)
 - b. Compound dose response evaluations are performed at 6 different concentrations (10 μ M, 1 μ M, 100 nM, 10 nM, 1 nM, and 0.1 nM);
 - c. Triplicates wells are run for each compound concentration.
- 10 3. In the absence of mitogen:
 - a. Next day, remove the old medium and add compounds in fresh medium (without mitogen)
 - b. Compound dose response evaluations are performed at 6 concentrations (10 μ M, 1 μ M, 100 nM, 10 nM, 1 nM, and 0.1 nM);
 - 15 c. Triplicates wells are run for each compound concentration.
4. Culture the treated cells for 7 d prior to using in experimental assays.

HUMAN Oligodendrocyte cultures

Preparation of cells:

- 20 1. Human neurospheres collected from E19.5 – E22 human embryo cortex) are cultured for 2 weeks in progenitor media: DMEM/F12 containing 100 μ g/ml transferring, 30 nM triiodothyronine, 20 nM hydrocortisone, 20 nM progesterone, 10 nM biotin, 1x trace elements, 30 nM selenium, 60 μ M putrescine, 0.1% BSA, 5 U/ml PenStrep, 25 μ g/ml insulin) supplemented with PDGF and FGF.
- 25 2. Neurospheres are dissociated with 20 U/ml papain at 37°C for 30-50 min.
3. Cells are plated onto PDL coated dishes at density of 50,000-100,000 cell/well in progenitor media containing PDGF/FGF and incubated at 37°C with 5-6% CO₂.
4. Media and growth factors are replenished every 48 hr.

30 **Human Culture Compound Treatment:**

1. 24 to 48 hr after plating remove the old medium and add compounds in fresh medium (with mitogen)

2. Compound dose response evaluations are performed at 3-6 different concentrations (10 μ M, 1 μ M, 100 nM, 10 nM, 1 nM, and 0.1 nM)
3. Triplicates wells are run for each compound concentration.
5. Culture the treated cells for 7 d prior to using in experimental assays.

5

RAT/MOUSE/HUMAN Oligodendrocyte Specific Immunostaining:

Following compound exposure, oligodendrocyte-specific antibodies are used to assess ability of compound to accelerate/promote oligodendrocyte differentiation (for example, O4, O1, or myelin basic protein immunoreactivity is over time between compound treated and untreated cultures).

10

1. Cells are plated onto poly-D-lysine treated 4-well chamber slides at 5×10^3 to 20×10^3 cells/well and grown as described above. Sequential staining is performed on oligodendrocyte populations with increasing degrees of cellular differentiation, as determined by days *in vitro* without PDGF and FGF.
- 15 2. Live staining for 30 min at 37°C is used to detect oligodendrocyte stage specific cell surface marker expression (including A2B5, O4, and O1).
3. Subsequently, cells are fixed with 4% paraformaldehyde, 10 min, room temperature.
4. Fixed staining procedures are used to detect oligodendrocyte stage specific marker expression (including myelin basic protein, MBP).
- 20 5. Rinse with PBS.
6. Permeabilize with 0.1% Triton/0.01% NaAz diluted in 1X PBS for 10 min, room temperature.
7. Block with 5-10% goat serum in antibody dilution buffer (0.1% Triton-X 100 and 1% IgG-free bovine serum albumin; also used to dilute antibodies), 15 min, room temperature.
- 25 8. Add primary antibody diluted in antibody dilution buffer.
9. Incubate overnight, gently rocking, 4°C.
10. Next day, rinse with PBS 1X 5 min, followed by 3X 15 min each, room temperature.
11. Incubate with appropriate secondary antibodies, 45 min, room temperature.
- 30 12. Cell nuclei are stained with 4,6-diamidino-2-phenylindole (DAPI), 15min, room temperature.
13. Rinse several times with PBS and evaluate using fluorescent microscopy.

14. The following conditions are compared over time and at different compound doses:

PDGF/FGF alone, SFM alone, SFM-IGF1 alone, PDGF/FGF and compound, SFM and compound.

RAT/MOUSE/HUMAN Bromodeoxyuridine (BrdU) immunostaining:

To confirm that compounds do not promote cell proliferation.

1. Oligodendrocyte progenitor cells are labeled with 10 μ M BrdU for 20 hr and then fixed with either 70% ethanol or 4% paraformaldehyde.
2. The cells are incubated successively with biotinylated mouse anti-BrdU and Streptavidin-Peroxidase, with three intervening washes with PBS.
3. Colormetric visualization of the BrdU immunoreactivity is developed with DAB and total cell numbers are assessed using the counter-stain hematoxylin.
4. BrdU immunopositive cells are counted by two independent observers.

RAT/MOUSE/HUMAN Culture Image analysis: Fluorescent microscopy is used to quantitate

the extent of oligodendrocyte differentiation after compound exposure. This assay demonstrates that selective agonists accelerate/promote oligodendrocytes differentiation.

1. Manual Cell Counting: Four fields are randomly selected for each experimental condition and 500-600 cells are counted in each field. The percentage of MBP (or O4) immunopositive cells (mature process bearing cells with or without myelin sheaths) versus DAPI positive cells (total cell number) cells are compared in the control and drug-treated groups.
2. Automated Cell Counting: Fluorescent microscopy was used to quantitate the extent of oligodendrocyte differentiation after compound exposure. Six fields/well were randomly selected to assess the number of differentiating oligodendrocytes among the total population (~8 to 15x10³ cells are counted/well). Immunofluorescence images were obtained using a Zeiss AxioVision digital imaging system, with a Zeiss AxioCam HRc cooled CCD camera connected to the same microscope. All microscopic imaging parameters were set for acquiring images for the analysis of cellular immunofluorescence intensity. The percentage of MBP positive (differentiated) cells versus total cells (DAPI nuclear stained) was compared in the control versus drug-treated groups. Cellular autofluorescence was undetectable under the imaging conditions.

3. Human oligodendrocyte differentiation assay: manually count total number of O4 immunopositive cells/well (bipolar and multipolar).

The results using rat oligodendrocyte cultures are shown in Table 2. As the results show compounds of the instant invention enhance or accelerate rat oligodendrocyte differentiation, as measured by increased myelin basic protein expression compared to untreated controls. This finding suggests compound examples shown in Table 2 would enhance, accelerate, or stimulate oligodendrocyte differentiation and myelin formation *in vivo*, in the diseased or injured CNS, including MS and other demyelinating disorders.

Table 2

Results for Compounds in Primary Rat Oligodendrocyte Differentiation Assay

Example No.	Fold Increase in Myelin Basic Protein Expression in Oligodendrocyte Differentiation Assay (concentration μ M)
10	1.5 fold (10)
14	1.5 fold (1)
23	2 fold (1)
31	2 fold (1)

RAT/MOUSE/HUMAN Quantitative Polymerase Chain Reaction (PCR): To evaluate compound induced PPAR delta pathway activation and the extent of oligodendrocyte maturation (changes in mRNA levels).

1. Total RNA is extracted from cultured oligodendrocytes using TriZol reagent.
2. Subsequently, mRNA is treated with RNase-free DNase, repurified, and then converted to cDNA template using a RT reaction (Clontech Advantage RT for PCR Kit).
3. PPAR delta pathway member transcript expression is quantitated using Sybr Green PCR Master Mix.
4. The 18S ribosomal RNA primer/probe mix (186 bp product), suspended in Taqman 2X PCR Master Mix is used as an internal control.

5. Quantitative PCR is carried out using real-time Taqman™ technology (Gibson, et al., 1996) with a model 7700 Sequence Detector System (Applied Biosystems, Foster City, CA).
6. The results are analyzed using Sequence Detection Systems software version 1.91.

5

RAT ELISA Assay: To evaluate compound induced PPAR delta pathway activation and the extent of oligodendrocyte maturation (changes in protein levels).

1. Plates are washed with PBS, and then keep on ice. Add 200 µl ice cold lysis buffer (Tris 50mM, pH7.4, MgCl₂ 2mM, EDTA 1mM, β-mercaptoethanol 5mM, Nonidet P-40 1%, Protease inhibitor cocktail (Roche): 1 tablet/50 ml) to each well.
- 10 2. Lyse cells by using pipette to up down and spin plates at 2000 rpm at 4°C for 5 min. The supernatant is ready to use.
3. Pipet 50 µl of standard, controls and samples to the wells.
4. Add 50 µl of MBP Assay Buffer to each well.
- 15 5. Incubate the well, shaking at 500-700 rpm on orbital microplate shaker for 2 hr at room temperature.
6. Add 100ul of the MBP Antibody-Biotin Conjugate to each well.
7. Incubate the well, shaking at 500-700 rpm on orbital microplate shaker for 1 hr at room temperature.
- 20 8. Wash well 5 times with Wash Solution. Blot dry by inverting the plate on absorbent material.
9. Dilute the streptavidin-enzyme conjugate concentrate 1:50 with MBP Elisa Assay buffer. (must be diluted immediately prior to use in the assay).
10. Add 100 µl streptavidin-enzyme conjugate solutions to each well.
- 25 11. Incubate the well, shaking at 500-700 rpm on orbital microplate shaker for 30 min at room temperature.
12. Wash well 5 times with the Wash Solution. Blot dry by inverting the plate on absorbent material.
13. Add 100 µl of TMB Chromogen Solution to each well.
- 30 14. Incubate the well, shaking at 500-700 rpm on orbital microplate shaker for 10-20 min at room temperature. Avoid exposure to direct sunlight.
15. Add 100 µl of the Stopping Solution to each well.

Read the absorbance of the solution in the wells within 30 min, using a microplate reader set to 450 nM

In Vivo Proof of Concept Models

5 Focal Lesions; (used to assess whether compounds protect myelin integrity or accelerate/enhance the rate of remyelination.)

1. Rats 7 weeks of age are given free access to food and water and acclimatized for a minimum of 4 days before use in experiments.
2. Prior to surgery each animal is weighed. The rat is then anaesthetized with ketamine (100 mg/ml) in combination with xylazine (20 mg/ml) in a ratio of 1.8 : 1. The rats are
10 injected with 0.15ml/180g body weight i.p. of the anaesthetic solution prior to the surgical procedure. The animal is prepared for surgery using aseptic conditions in accordance with the IACUC guidelines. All surgical instruments will be autoclaved. The hair is clipped between the ears and this region will then be scrubbed with
15 Betadine, flushed with sterile saline and finally wiped with a pre-packaged sterile alcohol swab.
3. For the surgical procedure, the rat is placed on its ventral surface in a small animal stereotaxic instrument designed to hold the head steady. The incisor bar is always set at -3.9 mm, since this has been shown to achieve a flat-skull position for SD rats.
- 20 4. An incision is made in the previously shaven skin overlying the skull between the ears.
5. A small area of bone (0.75mm in diameter) is drilled at the following coordinates AP -- 1.8, ML -3.1 from lambda.
6. The bone is removed and rats are injected with 2µl ethidium bromide, lysolecithin, or SIN-1 into the right caudal cerebellar peduncle, DV -7.1 mm, over a 2 min period by
25 means of a Hamilton µl syringe and needle. Alternatively injections are made into the spinal cord, corpus callosum, or cortex.
7. The needle is left in position for the subsequent 2 min.
8. After withdrawal of the needle the incision is sutured.
9. Each rat receives an i.m. injection of 0.003mg buprenorphine into a hind leg.
- 30 10. The rat is placed in a warming cupboard until it regains consciousness. At which time it is returned to its home cage. Do not allow more than 2 rats per cage, as they will pull each other's suture out.
11. Similar procedures are also done using mice.

Rat Experimental Allergic Encephalomyelitis (Rat EAE) Disease Model:

Experimental allergic encephalomyelitis (EAE) is a T-cell-mediated autoimmune disease of the nervous system that develops in susceptible animals following sensitization with either whole spinal cord homogenate or a component (myelin basic protein). The EAE rodent model is an appropriate tool for studying the inflammation of the brain and spinal cord observed in MS patients. In rodents, injection of whole spinal cord or spinal cord components such as myelin basic protein induces an autoimmune response based on the activation of T-lymphocytes. Clinical disease typically becomes manifest around day 8-10 after inoculation, observed as a broad spectrum of behavioral anomalies ranging from mild gait disturbances and tail atony to complete paralysis and death. Weight loss typically occurs. In animals that survive, spontaneous recovery occurs, accompanied by variable recovery of most motor function. Depending on the species, allergen, and methodology used, animals tested by the EAE model may experience a single (acute EAE) or several (chronic relapsing EAE) attacks. Several treatment paradigms may be used: the drug or treatment of choice may be administered before immunization, during the nonsymptomatic period or during the clinical disease.

Animals:

Female Lewis rats, 160-220g (Charles River)

Antigen:

Whole Guinea Pig spinal cord (Harlan Biosciences).

Complete Freund's adjuvant H37 Ra [1mg/ml Mycobacterium Tuberculosis H37 Ra] (Difco).

Additional antigen:

Mycobacterium Tuberculosis (Difco).

Bordetella Pertussis [Heat Killed] (Difco).

Antigen preparation: (for approximately 720 animals):

1. Weigh 5 grams of frozen guinea pig spinal cord.
2. Add 5g spinal cord to 5ml 0.9% saline (1g/ml) in a round bottom centrifuge tube
3. Homogenize on ice with the Tissue-tech until the tissue is completely disrupted (approximately 5 minutes).

4. Add 10 ml Complete Freund's adjuvant H37 Ra supplemented with 200 mg Mycobacterium Tuberculosis (20 mg / ml Complete Freund's adjuvant H37 Ra).
5. Extract homogenate / adjuvant from tube by sucking it into a 10 ml syringe fitted with an 18 gauge emulsifying needle.
- 5 6. Emulsify between two 30 ml glass syringes until it becomes difficult to continue passing the material through the needle. (Approximately 5 minutes (there must be no separation between the oil phase and the aqueous phase)).
7. Use immediately or keep on ice until needed (not more than 30 min) (do not freeze).

10

Protocol

1. Female Lewis rats (Charles River) are given free access to food and water and should be acclimated a minimum of 3 days before use in experiments.
2. Rats weighing 160 and 220 grams are initially induced with 5% isoflurane (Aerrane, Fort Dodge), 30% O₂, 70% N₂O for 2-5 minutes.
- 15 3. The rat is then placed onto a circulating water heating blanket (Gaymar) (dorsal surface up) and into the nose cone for spontaneous respiration of anesthetic gases. The isoflurane is reduced to 2%.
4. Two subcutaneous injections (0.1 ml each) of either antigen or normal saline are made into ventral surface of the hind paws.
- 20 5. The animals are removed from the nose cone, weighed and numbered.
6. The rats are allowed to awake from anesthesia and are placed into individual cages.
7. The animals are observed daily for signs of EAE induction (see criteria below)

STAGE:0 NORMAL

25

STAGE 1 Abnormal gate and tail atony

STAGE 2 Mild but definite weakness of one or both hind legs

STAGE: 3 Severe weakness of one or both hind legs or mild ataxia

STAGE: 4 Severe paraparesis and minimal hind leg movement

STAGE: 5 No hind leg movement and paraplegia

30

STAGE: 6 Moribund state with no spontaneous movement and impaired respiration.

Increasing degree of front leg involvement and urinary and fecal incontinence may also occur

STAGE:7 DEATH

Treatment is begun on day 10 after immunization. Since the disease symptoms in this model typically appear 10-11 days after inoculation, this time point may be considered to represent the initial phase of an acute episode of MS. It is judged that this delay of the start of treatment mimics the clinical situation more closely than the traditionally used protocols where drugs are administered at the time of, or even before, inoculation (Teitelbaum D. et al., Proc Natl Acad Sci USA 1999; 96: 3842-3847 and Brod S. A., et al., Ann Neurol 2000; 47: 127-131).

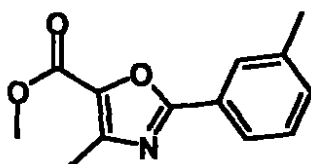
This invention is further illustrated by the following examples of compounds used herein which are provided for illustration purposes and in no way limit the scope of the present invention.

Synthetic Examples

General

Commercial reagents and solvents were used as received. ¹H NMR spectra were recorded on a Varian MercuryPlus-300 (300 MHz) or Varian Unity Inova (400 MHz) spectrometer as indicated. Proton chemical shifts are reported in δ ppm relative to internal tetramethylsilane (0.0 ppm). MS (LC-MS) data is obtained using a Micromass LCT time of flight mass spectrometer with electrospray ionization and 5 min data acquisition time for m/z 100 to 1000. LC (LC-MS) is performed using a Hypersil C18 column (4.6x50mm, 3.5 μ m) with mobile phase of 0.1 % TFA in H₂O (A) and 0.1% TFA in ACN (B) and a gradient of 5% to 100% B over 3 min followed by 2 min at 100% B. Alternatively, a Platform LC-MS with electrospray source may be used with a HP1100 LC system running at 2.0 ml/min, 200 μ L/min split to the BSI source with inline HP1100 DAD detection and SEDEX ELS detection. A Luna C18(2) column (30x4.6mm 3 μ m) is used with a gradient of 5% to 95% B over 4.5 min with mobile phase of 0.1% formic acid in H₂O and 0.1% formic acid in ACN (B). HPLC purification is performed on a Varian ProStar system using a reversed-phase C18 column with a linear gradient of ACN /H₂O containing 0.1% trifluoroacetic acid. Microwave syntheses were performed using a Personal Chemistry Smithcreator microwave reaction system using 2 or 5 mL reactor vessels.

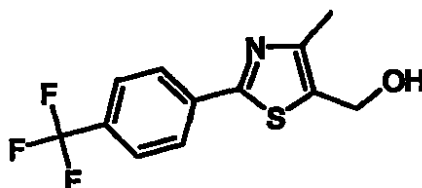
Example 1



Intermediate: 4-Methyl-2-*m*-tolyl-oxazole-5-carboxylic acid methyl ester

- 5 Heat to 120°C a neat mixture of methyl 2-chloroacetoacetate (914 mL, 7.5 mmol) and 3-methyl-benzamide (676 mg, 5 mmol) and stir at this temperature for 12 hrs. Cool the reaction mixture to room temperature and dilute it with ethyl acetate, wash with saturated sodium bicarbonate solution (3 times), water (twice) and brine, Dry the organic extract over MgSO₄ and concentrate. Purify the resulting residue by flash chromatography (elute with
10 10% ethyl acetate in heptane) to give the title compound as a yellow oil (492 mg).

Example 2

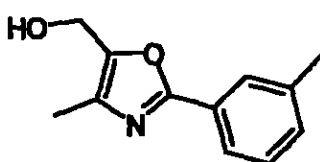


15

Intermediate: [4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol

- Cool (0°C) a solution of lithium aluminum hydride (10 mL, 1M in THF) and add a solution of 4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-carboxylic acid (Commercially
20 available, 2.87g, 10 mmol) in THF (20 mL). On complete addition, remove the cold bath and stir for 3.5 hrs. Cool this solution to 5°C, and then add water (0.25 mL), dropwise, followed by NaOH solution (0.25 mL, 5M in water) and water (0.5 mL). Dilute the resulting mixture with ethyl acetate and then filter through a pad of celite. Wash the solids with dichloromethane and then concentrate the combined filtrates under reduced pressure to give the title compound as a
25 yellow solid (2.59 g).
- MS (ESI) *m/z* 274 (M+H); ¹H NMR (CDCl₃) δ 1.87 (bs, 1H), 2.49 (s, 3H), 4.86 (s, 2H), 7.67 (d, *J* = 8Hz, 2H), 8.02 (d, *J* = 8Hz, 2H).

Example 3

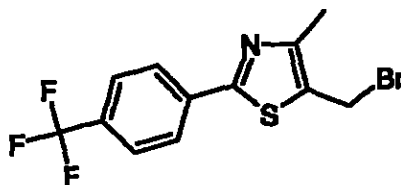


5 Intermediate: [4-Methyl-2-*m*-tolyl-oxazol-5-yl]-methanol

Follow the procedure of Example 2, but use the compound of Example 1 as the starting material to obtain the title compound.

MS (ESI) m/z 204 (M+H); ^1H NMR (CDCl_3) δ 2.25 (s, 3H), 2.40 (t, $J = 7\text{Hz}$, 1H), 2.42 (s, 3H), 4.70 (d, $J = 7\text{Hz}$, 2H), 7.25-7.36 (m, 2H), 7.75-7.85 (m, 2H).

Example 4

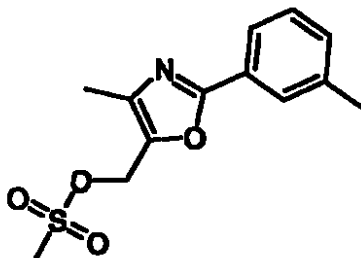


15 Intermediate: 5-Bromomethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole

Cool (10°C) a solution of [4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methanol (Example 2, 753 mg, 3 mmol) in THF (12 mL) add triphenylphosphine (864 mg, 3.3 mmol) followed by freshly recrystallized *N*-bromosuccinimide (587 mg, 3.3 mmol). On complete addition, remove the cold bath and stir continuously for 45 min. Concentrate the resulting mixture under vacuum and purify the residue by flash chromatography (elute with 10% ethyl acetate / 10% dichloromethane in heptane) to give the title compound as an orange solid (846 mg).

25 MS (ESI) m/z 336,338 (M+H); ^1H NMR (CDCl_3) δ 2.48 (s, 3H), 4.72 (s, 2H), 7.69 (d, $J = 8\text{Hz}$, 2H), 8.01 (d, $J = 8\text{Hz}$, 2H).

Example 5



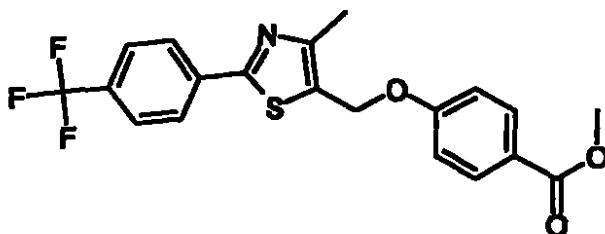
Intermediate: Methanesulfonic acid [2-(3-methyl-phenyl)-4-methyl oxazol-5-yl]-methyl ester

5

Cool (0°C) a solution of [2-(3-methyl-phenyl)-4-methyl oxazol-5-yl]-methanol (Example 3, 756 mg, 4 mmol) in dichloromethane (16 mL) and add, sequentially, DMAP (51 mg, 0.4 mmol), triethylamine (552 µL, 4 mmol) and methanesulfonyl chloride (323 µL, 4.2 mmol). Stir the resulting solution for 5 min., remove the cooling bath and stir for 25 min.

10 Dilute this solution with ether, wash with hydrochloric acid (5 mL, 2M), brine, dry over MgSO₄ and concentrate to give the title compound (743 mg).

Example 6



15

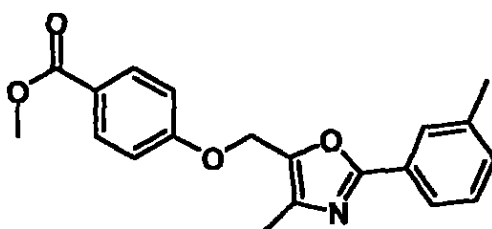
Intermediate: 4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzoic acid methyl ester

20 To a mixture of 4-hydroxy-benzoic acid methyl ester (152 mg, 1 mmol) and potassium carbonate (152 mg, 1.1 mmol) add acetonitrile (4 mL). To this mixture add 5-bromomethyl-4-methyl-2-(4-trifluoromethyl-phenyl)-thiazole (Example 4, 314 mg, 1 mmol). Warm the resulting reaction mixture to 60°C, and stir at this temperature for 5 hrs. Cool the mixture to room temperature, dilute with ethyl acetate, wash with water, then brine, dry over MgSO₄,

25 filter and concentrate to give the title compound as a white solid (364 mg).

MS (ESI) m/z 408 (M+H); ^1H NMR (CDCl_3) δ 2.53 (s, 3H), 3.90 (s, 3H), 4.52 (s, 2H), 7.00 (d, $J = 9\text{Hz}$, 2H), 7.68 (d, $J = 8\text{Hz}$, 2H), 8.02 (m, 4H).

Example 7

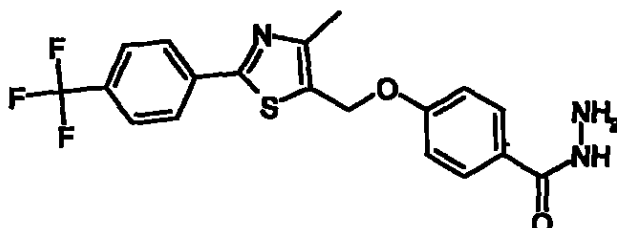


Intermediate: 4-(4-Methyl-2-m-tolyl-oxazol-5-ylmethoxy)-benzoic acid methyl ester

Follow the procedure of Example 6, but use the compound of Example 5 as the starting material to obtain the title compound.

MS (ESI) m/z 338 (M+H); ^1H NMR (CDCl_3) δ 2.30 (s, 3H), 2.41 (s, 3H), 3.90 (s, 3H), 5.11 (s, 2H), 7.03 (d, $J = 9\text{Hz}$, 2H), 7.25 (m, 1H), 7.33 (t, $J = 8\text{Hz}$, 1H), 7.81 (d, $J = 8\text{Hz}$, 1H) 7.87 (bs, 1H) 8.02 (d, $J = 9\text{Hz}$, 2H).

Example 8



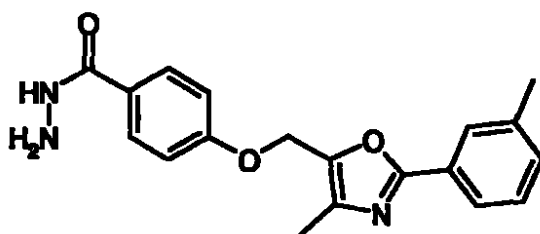
Intermediate: 4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzoic acid hydrazide

To a suspension of 4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzoic acid methyl ester (Example 6, 364 mg, 1 mmol) in methanol (10 mL) add anhydrous hydrazine (128 mL, 4 mmol). Warm the resulting mixture to 60°C and stir at this temperature for 18 hrs. Cool the resulting solution to room temperature, and add 3 drops of water.

Concentrate the solution under vacuum and purify the residue by flash chromatography (elute with 5% methanol in dichloromethane) to give the title compound (271 mg).

MS (ESI) m/z 408 (M+H); ^1H NMR (DMSO) δ 2.51 (s, 3H), 4.4 (bs, 2H), 5.42 (s, 2H) 7.10 (d, $J = 9\text{Hz}$, 2H), 7.82 (d, $J = 9\text{Hz}$, 2H), 7.85 (d, $J = 8\text{Hz}$, 2H) 8.12 (d, $J = 8\text{Hz}$, 2H) 9.63 (bs, 1H).

Example 9

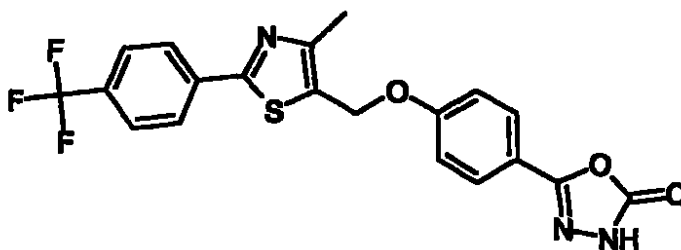


Intermediate: 4-(4-Methyl-2-m-tolyl-oxazol-5-ylmethoxy)-benzoic acid hydrazide

Follow the procedure of Example 8, but use the compound of Example 7 as the starting material to obtain the title compound.

MS (ESI) m/z 338 (M+H); ^1H NMR (DMSO) δ 2.24 (s, 3H), 2.38 (s, 3H), 4.43 (bs, 2H), 5.26 (s, 2H) 7.11 (d, $J = 9\text{Hz}$, 2H), 7.34 (d, $J = 8\text{Hz}$, 1H), 7.41 (t, $J = 8\text{Hz}$, 1H) 7.74-7.83 (m, 4H) 9.63 (bs, 1H).

Example 10

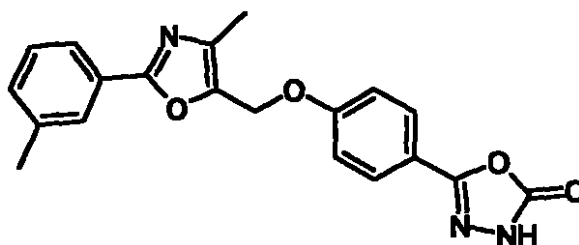


5-[4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl]-3H-[1,3,4]oxadiazol-2-one

To a suspension of 4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzoic acid hydrazide (Example 8, 271 mg, 0.74 mmol) in dichloromethane (7 mL) add phenylchloroformate (94 μ L, 0.75 mmol) followed by pyridine (132 μ L, 1.63 mmol). Stir the resulting mixture at room temperature until all the starting material is consumed (by TLC analysis). Concentrate the mixture, and then take the residue up in acetonitrile (10 mL). To this mixture, add DBU (220 μ L, 1.5 mmol). Seal the resulting solution; warm it to 180°C in a Personal Chemistry™ microwave oven and stir at this temperature for 15 min. Cool the reaction to room temperature, dilute with ethyl acetate, wash with 1 M HCl solution (or saturated NaH₂PO₄ solution) dry over MgSO₄ and concentrate. Triturate the resulting residue with dichloromethane several times to give the title compound as a tan solid (69 mg).

MS (ESI) m/z 365 (M+H); ¹H NMR (DMSO) δ 2.51 (s, 3H), 4.4 (bs, 2H), 5.42 (s, 2H) 7.10 (d, J = 9Hz, 2H), 7.82 (d, J = 9Hz, 2H), 7.85 (d, J = 8Hz, 2H) 8.12 (d, J = 8Hz, 2H) 9.63 (bs, 1H).

Example 11

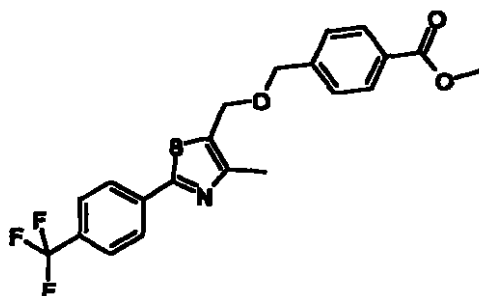


5-[4-(4-Methyl-2-m-tolyl-oxazol-5-ylmethoxy)-phenyl]-3H-[1,3,4]oxadiazol-2-one.

Follow the procedure of Example 10, but use the compound of Example 9 as the starting material to obtain the title compound.

MS (ESI) m/z 364 (M+H); ¹H NMR (DMSO) δ 2.25 (s, 3H), 2.38 (s, 3H), 5.30 (s, 2H) 7.23 (d, J = 9Hz, 2H), 7.34 (d, J = 8Hz, 1H), 7.41 (t, J = 8Hz, 1H) 7.75-7.79 (m, 4H) 12.44 (bs, 1H).

Example 12



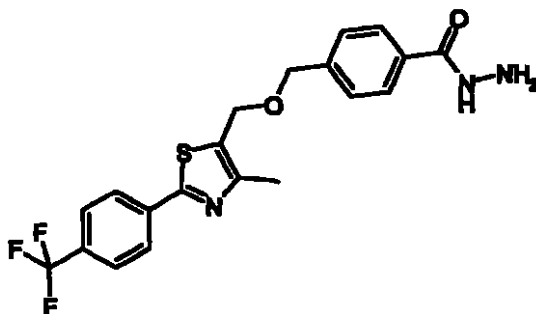
5 Intermediate: 4-([4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxymethyl)-benzoic acid methyl ester

10 Cool (-5°C) a suspension of NaH (84mg, 60% dispersion in mineral oil, 2.05 mmol) in THF (4 mL) and add a solution comprised of 2-([4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl)-methanol (546 mg, 2 mmol) and 4-bromomethyl-benzoic acid methyl ester (458 mg, 2 mmol) in THF (5 mL). Stir the resulting mixture for 5 min then the remove the cold bath and stir for an additional 3hr. Quench the reaction with 1M HCl solution, dilute with ethyl acetate, wash with brine and dry over Mg SO₄. Concentrate this solution under vacuum
15 and purify the residue by flash chromatography (eluting with 20% ethyl acetate in heptane) to give the product (377 mg) as a white solid.

MS (ESI) *m/z* 422 (M+H); ¹H NMR (CDCl₃) δ 2.44 (s, 3H), 3.92 (s, 3H), 4.64 (s, 2H), 4.71 (s, 2H), 7.42 (d, *J* = 8Hz, 2H), 7.66 (d, *J* = 8Hz, 2H) 8.00 (m, 4H).

20

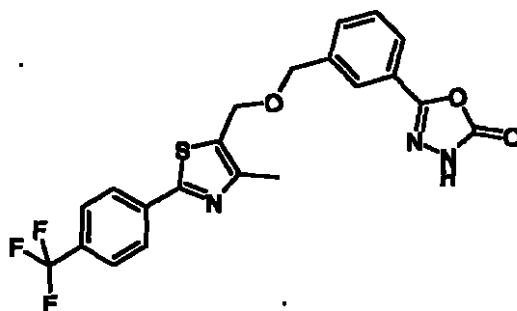
Example 13



Intermediate: 4-([3-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxymethyl)-benzoic acid hydrazide

Follow the procedure of Example 8, but use the compound of Example 15 as the starting material to obtain the title compound.

Example 17

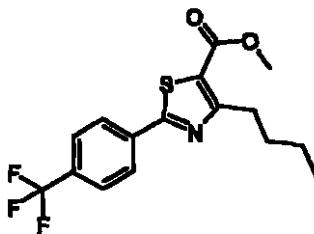


5-{3-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxymethyl}-phenyl]-3H-[1,3,4]oxadiazol-2-one

Follow the procedure of Example 10, but use the compound of Example 16 as the starting material to obtain the title compound.

MS (ESI) m/z 448 (M+H); ^1H NMR (DMSO) δ 2.40 (s, 3H), 4.65 (s, 2H), 4.79 (s, 2H), 7.53 (m, 2H), 7.72 (m, 1H), 7.77 (s, 1H), 7.82 (d, $J = 8\text{Hz}$, 2H), 8.10 (d, $J = 8\text{Hz}$, 2H), 12.5 (bs, 1H).

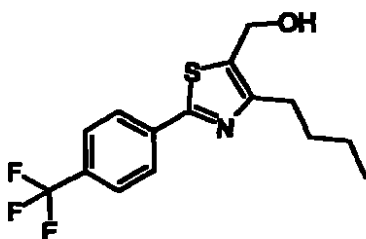
Example 18



Intermediate: 4-Butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-carboxylic acid methyl ester

To a solution of 3-oxo-heptanoic acid methyl ester (5.0 g, 31.6 mmol) in dry dichloromethane (80 mL) add sulfurylchloride (2.82 mL). Stir the reaction mixture at room temperature for 30 minutes then add water (20 mL) and the reaction mixture extracted five times with portions of 30 mL of dichloromethane. Wash the combined organic extracts with water, saturated aqueous solution of NaHCO₃ and brine and then dry over MgSO₄. Remove the solvent under reduced pressure to give 2-chloro-3-oxo-heptanoic acid methyl ester (6.0 g), which was used in the next step without further purification. To a solution of 2-chloro-3-oxo-heptanoic acid methyl ester (6.0 g, 31.1 mmol) in ethanol (50 mL) add 4-(trifluoromethyl)thiobenzamide (6.4 g, 31.2 mmol). Heat the reaction mixture to reflux overnight. Remove the solvent under reduced pressure and purify the residue by chromatography on silica gel (eluting with a gradient of n-heptane:ethyl acetate (100:1 to 60:1)) to give 4-butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5- carboxylic acid methyl ester (7.4 g) as a yellow oil. MS (ESI) *m/z* 344 (M+H).

Example 19



Intermediate: [4-Butyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-yl]-methanol

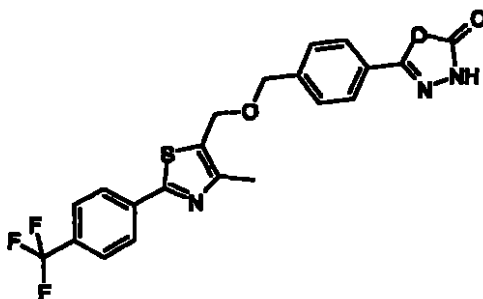
To a solution of lithium aluminium hydride (1.2 g) in dry tetrahydrofuran (100 mL) add 4-butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5- carboxylic acid methyl ester (5.3 g, 15.4 mmol) dissolved in tetrahydrofuran (100 mL). Stir the reaction mixture at room temperature over a period of one hour. Add a saturated aqueous solution of ammonium chloride (50 mL) and then a 1 molar aqueous solution of hydrochloric acid (50 mL). Extract the reaction mixture five times with portions of 60 ml of ethyl acetate. Dry the combined extracts with MgSO₄ and remove the solvent under reduced pressure to provide [4-butyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-yl]-methanol (4.6 g) as a yellow oil, which solidified upon standing at room temperature.

Intermediate: 4-([4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxymethyl)-benzoic acid hydrazide

Follow the procedure of Example 8, but use the compound of Example 12 as the starting material to obtain the title compound.

MS (ESI) m/z 422 (M+H); ^1H NMR (CDCl_3) δ 2.44 (s, 3H), 4.09 (bs, 2H), 4.63 (s, 2H), 4.71 (s, 2H), 7.30 (bs, 1H), 7.44 (d, $J = 8\text{Hz}$, 2H), 7.66 (d, $J = 8\text{Hz}$, 2H), 7.73 (d, $J = 8\text{Hz}$, 2H) 8.00 (d, $J = 8\text{Hz}$, 2H).

Example 14

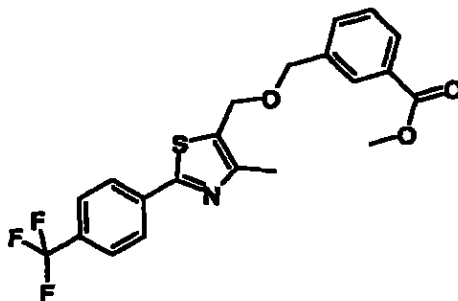


5-([4-[4-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-methoxymethyl]-phenyl)-3H-[1,3,4]oxadiazol-2-one

Follow the procedure of Example 10, but use the compound of Example 13 as the starting material to obtain the title compound.

MS (ESI) m/z 448 (M+H); ^1H NMR (DMSO) δ 2.40 (s, 3H), 4.65 (s, 2H), 4.78 (s, 2H) 7.50 (d, $J = 8\text{Hz}$, 2H), 7.78 (d, $J = 8\text{Hz}$, 2H), 7.82 (d, $J = 8\text{Hz}$, 2H) 8.10 (d, $J = 8\text{Hz}$, 2H) 12.54 (bs, 1H).

Example 15



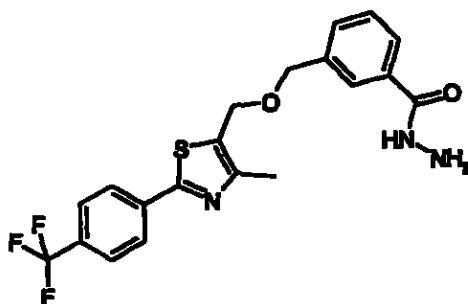
5 Intermediate: 4-(13-Methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl)-methoxymethyl]-
benzoic acid methyl ester

Cool (0°C) a solution of 2-([4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl]-
methanol (450 mg, 1.64 mmol) in THF and add NaH (70mg, 50% dispersion in mineral oil,
10 1.75 mmol). Stir the resulting mixture for 5 min. Remove the cold bath and continue stirring
for 1 hr. To this mixture add 3-(bromomethyl)-benzoic acid methyl ester (450mg, 1.95
mmol). Stir the resulting mixture for 3 hr then quench the reaction with sat. NH₄Cl solution.
Dilute the mixture with ether, wash with brine, dry over MgSO₄ and concentrate under
vacuum. Purify the residue by flash chromatography (eluting with 30% ethyl acetate in
15 heptane) to give the title compound (181 mg) as an oil.

MS (ESI) *m/z* 422 (M+H); ¹H NMR (CDCl₃) δ 2.44 (s, 3H), 3.92 (s, 3H), 4.63 (s, 2H), 4.71
(s, 2H) 7.44 (t, *J* = 8Hz, 1H), 7.56 (d, *J* = 8Hz, 1H), 7.66 (d, *J* = 8Hz, 2H), 7.00 (m, 4H).

Example 16

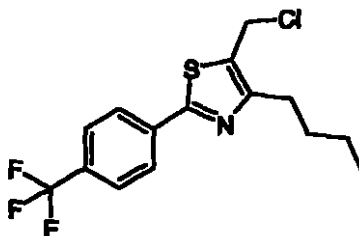
20



MS (ESI) m/z 316 (M+H); ^1H NMR (DMSO- d_6) δ 0,91 (t, $J = 7,0$ Hz, 3H), 1,35 (m, 2H), 1,64 (m, 2H), 2,70 (m, 2H), 4,68 (bm, 2H), 5,63 (bm, 1H), 7,83 (bd, $J = 8,5$ Hz, 2H), 8,09 (bd, $J = 8,5$ Hz, 2H).

5

Example 20



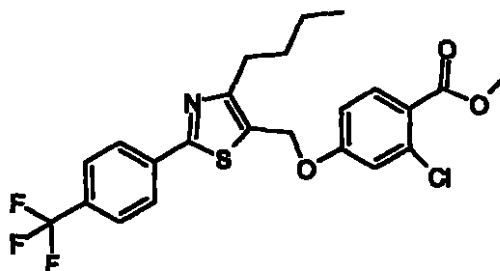
Intermediate: 4-Butyl-5-chloromethyl-2-(4-trifluoromethyl-phenyl)-thiazole

10 To a solution of [4-butyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-yl]-methanol (1.0 g, 3.1 mmol) in dichloromethane (50 mL) add triethylamine (0.88 mL) and methanesulfonyl chloride (0.39 mL). Stir the reaction mixture at room temperature for a period of three hours then add dichloromethane (100 mL). Wash the reaction mixture with a saturated aqueous solution of NaHCO_3 (50 mL), water and brine. Dry the organic layer over MgSO_4 and
15 remove the solvent under reduced pressure to give 4-butyl-5-chloromethyl-2-(4-trifluoromethyl-phenyl)-thiazole (1.0 g) as a yellow oil.

MS (ESI) m/z 334 (M+H); ^1H NMR (DMSO- d_6) δ 0,92 (t, $J = 7,5$ Hz, 3H), 1,37 (m, 2H), 1,68 (m, 2H), 2,80 (m, 2H), 5,14 (s, 2H), 7,86 (bd, $J = 8,5$ Hz, 2H), 8,12 (bd, $J = 8,5$ Hz, 2H).

20

Example 21

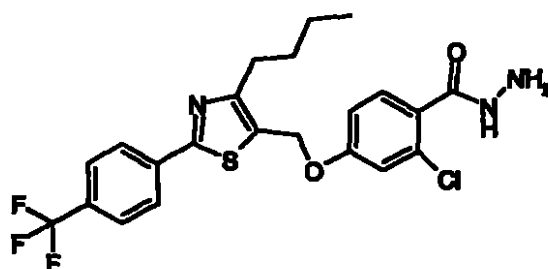


Intermediate : 4-[4-Butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-chloro-benzoic acid methyl ester

25

To an ice-cold solution of [4-butyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-yl]-methanol (1.0 g, 3.17 mmol), 2-chloro-4-hydroxy-benzoic acid methyl ester (592 mg, 3.17 mmol) and triphenylphosphine (832 mg, 3.17 mmol) in dichloromethane add diethyl azodicarboxylate (0.567 mL, 3.17 mmol). Stir the reaction mixture for 2 hours while allowing
5 it to warm to room temperature. Remove the solvent under reduced pressure and purify the residue by flash chromatography on silica gel to give 4-[4-butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-chloro-benzoic acid methyl ester (600 mg).
MS (ESI) m/z 484 (M+H).

Example 22

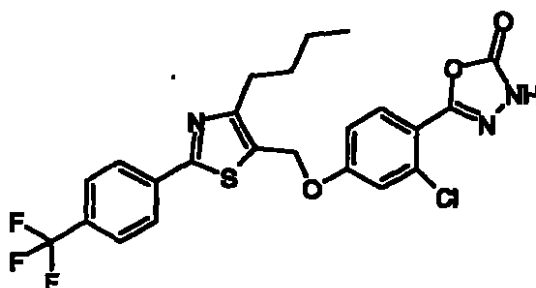


Intermediate : 4-[4-Butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-chloro-
15 benzoic acid hydrazide

Follow the procedure of Example 8, but use the compound of Example 21 as the starting material to obtain the title compound.

MS (ESI) m/z 484 (M+H).

Example 23

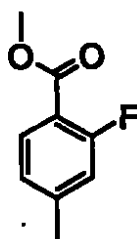


5-(4-[4-Butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-chloro-phenyl)-3H-[1,3,4]oxadiazol-2-one

Follow the procedure of Example 10, but use the compound of Example 22 as the starting material to obtain the title compound.

MS (ESI) m/z 510 (M+H); ^1H NMR (DMSO- d_6) δ 0.91 (t, 3H), 1.37 (m, 2H), 1.68 (m, 2H), 2.83 (t, 2H), 5.50 (s, 2H), 7.19 (dd, $J = 9, 2.5$ Hz, 1H), 7.40 (d, $J = 2.4$ Hz, 1H), 7.77 (d, $J = 8.6$ Hz, 1H), 7.86 (d, $J = 8.0$ Hz, 2H), 8.13 (d, $J = 8.3$ Hz, 2H), 12.64 (bs, 1H).

Example 24

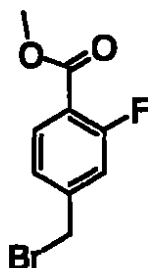


Intermediate: 2-Fluoro-4-methyl-benzoic acid methyl ester

To a solution of 2-fluoro-4-methyl-benzoic acid (1.1 g, 7.13 mmol) in methanol (20 mL) add thionyl chloride (1.02 g, 8.56 mmol). Stir the resulting mixture overnight then concentrate under vacuum to give the title compound (1.2 g) as a white solid.

MS (ESI) m/z 169 (M+H); ^1H NMR (DMSO- d_6) δ 2.37 (s, 3H), 3.83 (s, 3H), 7.12-7.21 (m, 2H), 7.79 (t, $J = 8.0$ Hz, 1H).

Example 25

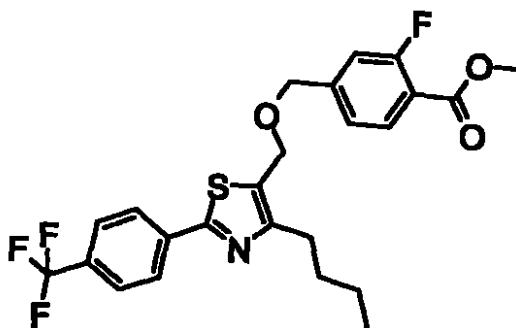


Intermediate: 4-Bromomethyl-2-Fluoro-benzoic acid methyl ester

To a solution of 2-fluoro-4-methyl-benzoic acid methyl ester (1.12 g, 6.66 mmol) in carbon tetrachloride (12 mL) add N-bromosuccinimide (1.18 g, 6.66 mmol) and benzoyl peroxide (10 mg). Heat the resulting mixture to 60°C for 15 hours then concentrate under vacuum to half and filter. Concentrate the filtrate under vacuum and purify the resulting crude product by flash chromatography on silica gel (eluting with 5/1 heptane/ethyl acetate) to give the title compound (1.35 g) as a white solid.

MS (ESI) m/z 247 (M+H); ^1H NMR (DMSO- d_6) δ 3.85 (s, 3H), 4.73 (s, 2H), 7.37-7.48 (m, 2H), 7.88 (t, J = 8.0 Hz, 1H).

Example 26



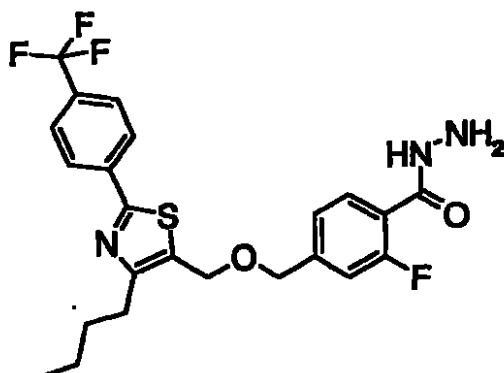
Intermediate: 4-[4-Butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxymethyl]-2-fluorobenzoic acid methyl ester

To a solution of [4-butyl-2-(4-trifluoromethyl-phenyl)-thiazole-5-yl]-methanol (1.02 g, 3.24 mmol) in anhydrous DMF (150 mL) add cesium carbonate (2.7 g, 8.10 mmol) and 4-bromomethyl-2-fluorobenzoic acid methyl ester (0.8 g, 3.24 mmol). Stir the resulting mixture overnight then pour into a 1M aqueous solution of potassium hydrogenophosphate and extracted three times with diisopropyl ether. Wash the combined extracts with water, dry over MgSO_4 , filter and concentrate under vacuum. Purify the residue by flash chromatography on silica gel (eluting with a gradient of heptane/ethyl acetate) to give the title compound (0.3 g) as a yellow solid.

MS (ESI) m/z 482 (M+H); ^1H NMR (DMSO- d_6) δ 0.89 (t, J = 7.5 Hz, 3H), 1.33 (m, 2H), 1.65 (m, 2H), 2.72 (m, 2H), 3.86 (s, 3H), 4.67 (s, 2H), 4.80 (s, 2H), 7.28-7.34 (m, 2H), 7.86 (bd, J = 8.5 Hz, 2H), 7.90 (t, J = 8.0 Hz, 1H), 8.11 (bd, J = 8.5 Hz, 2H).

-57-

Example 27

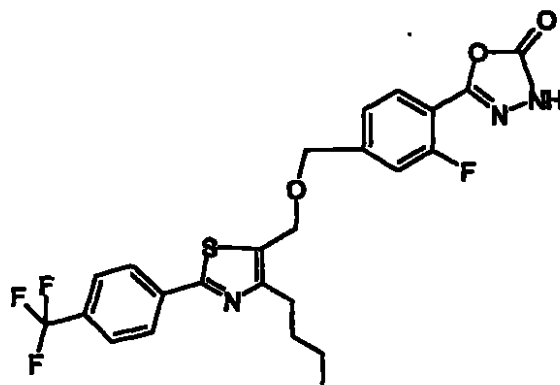


5 Intermediate: 4-[4-Butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxymethyl]-2-fluoro-
benzoic acid hydrazide

Follow the procedure of Example 8, but use the compound of Example 26 as the starting material to obtain the title compound.

10 MS (ESI) m/z 482 (M+H); ^1H NMR (DMSO- d_6) δ 0.90 (t, $J = 7.5$ Hz, 3H), 1.33 (m, 2H), 1.65 (m, 2H), 2.72 (m, 2H), 4.53 (bs, 2H), 4.62 (s, 2H), 4.79 (s, 2H), 7.20-7.29 (m, 2H), 7.57 (bt, $J = 8.0$ Hz, 1H), 7.84 (bd, $J = 8.5$ Hz, 2H), 8.12 (bd, $J = 8.5$ Hz, 2H), 9.51 (m, 1H).

Example 28



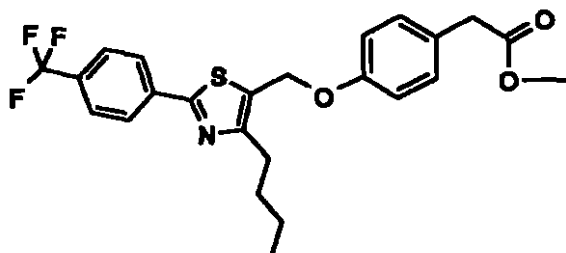
15 5-[4-[4-Butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxymethyl]-2-fluoro-phenyl]-
3H-[1,3,4]oxadiazol-2-one

20

Follow the procedure of Example 10, but use the compound of Example 27 as the starting material to obtain the title compound.

MS (ESI) m/z 508 (M+H); ^1H NMR (DMSO- d_6) δ 0.89 (t, $J = 7.5$ Hz, 3H), 1.33 (m, 2H), 1.65 (m, 2H), 2.73 (m, 2H), 4.68 (s, 2H), 4.81 (s, 2H), 7.33-7.40 (m, 2H), 7.80 (t, $J = 8.0$ Hz, 1H), 7.85 (bd, $J = 8.5$ Hz, 2H), 8.12 (bd, $J = 8.5$ Hz, 2H), 12.70 (bm, 1H).

Example 29

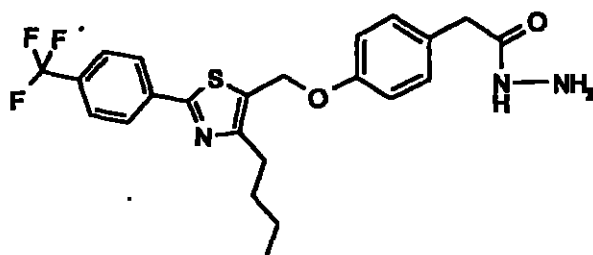


Intermediate: {4-[4-Butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxyl-phenyl]-acetic acid methyl ester

To a solution of 4-butyl-5-chloromethyl-2-(4-trifluoromethyl-phenyl)-thiazole (278 mg, 0.83 mmol) in anhydrous DMF (5 mL) add cesium carbonate (297 mg, 1.66 mmol) and methyl 4-hydroxyphenylacetate (200 mg, 1.20 mmol). Stir the resulting mixture overnight then pour into water and extract twice with ethyl acetate. Wash the combined extracts with water, dry over MgSO_4 , filter and concentrate under vacuum to give the title compound (290 mg) as a yellowish solid.

MS (ESI) m/z 508 (M+H); ^1H NMR (DMSO- d_6) δ 0.90 (t, $J = 7.5$ Hz, 3H), 1.36 (m, 2H), 1.67 (m, 2H), 2.80 (m, 2H), 3.60 (s, 3H), 3.61 (s, 2H), 5.33 (s, 2H), 7.00 (bd, $J = 8.5$ Hz, 2H), 7.21 (bd, $J = 8.5$ Hz, 2H), 7.84 (bd, $J = 8.5$ Hz, 2H), 8.12 (bd, $J = 8.5$ Hz, 2H).

Example 30



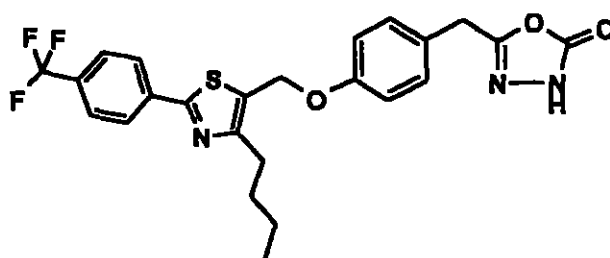
5 Intermediate: {4-[4-Butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-acetic acid hydrazide

Follow the procedure of Example 8, but use the compound of Example 29 as the starting material to obtain the title compound.

- 10 MS (ESI) m/z 464 (M+H); ^1H NMR (DMSO- d_6) δ 0.91 (t, $J = 7.5$ Hz, 3H), 1.36 (m, 2H), 1.67 (m, 2H), 2.80 (m, 2H), 3.28 (s, 2H), 4.17 (bd, $J = 4.0$ Hz, 2H), 5.32 (s, 2H), 6.97 (bd, $J = 8.5$ Hz, 2H), 7.19 (bd, $J = 8.5$ Hz, 2H), 7.84 (bd, $J = 8.5$ Hz, 2H), 8.12 (bd, $J = 8.5$ Hz, 2H), 9.13 (bt, $J = 4.0$ Hz, 1H).

15

Example 31



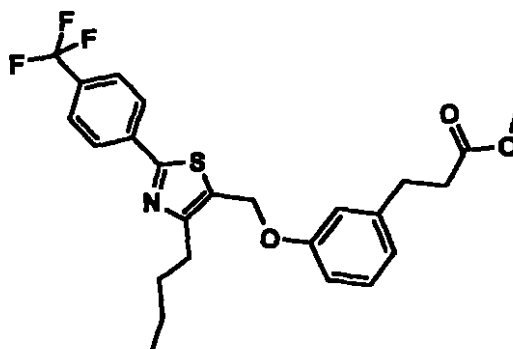
20 5-[4-[4-Butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-benzyl]-3H-[1,3,4]oxadiazol-2-one

Follow the procedure of Example 10, but use the compound of Example 30 as the starting material to obtain the title compound.

MS (ESI) m/z 490 (M+H); ^1H NMR (DMSO- d_6) δ 0.90 (t, $J = 7.5$ Hz, 3H), 1.36 (m, 2H), 1.68 (m, 2H), 2.80 (m, 2H), 3.87 (s, 2H), 5.33 (s, 2H), 7.03 (bd, $J = 8.5$ Hz, 2H), 7.24 (bd, $J = 8.5$ Hz, 2H), 7.85 (bd, $J = 8.5$ Hz, 2H), 8.12 (bd, $J = 8.5$ Hz, 2H), 11.7-12.4 (bm, 1H).

5

Example 32



Intermediate: 3-{3-[4-Butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl}-
propionic acid methyl ester

10

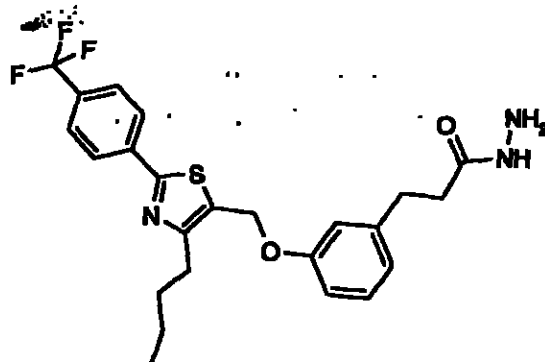
To a solution of 4-butyl-5-chloromethyl-2-(4-trifluoromethyl-phenyl)-thiazole (300 mg, 0.90 mmol) in anhydrous DMF (5 mL) add cesium carbonate (586 mg, 1.80 mmol) and methyl 3-(3-hydroxyphenyl)propionate (178 mg, 0.99 mmol). Stir the resulting mixture overnight then pour into water and extract twice with ethyl acetate. Wash the combined extracts with water, dry over MgSO_4 , filter and concentrate under vacuum. Purify the residue by flash chromatography on silica gel (eluting with 5% ethyl acetate in heptane) to give the title compound (290 mg) as a yellow oil.

15

MS (ESI) m/z 478 (M+H); ^1H NMR (DMSO- d_6) δ 0.91 (t, $J = 7.5$ Hz, 3H), 1.37 (m, 2H), 1.68 (m, 2H), 2.64 (m, 2H), 2.76-2.88 (m, 4H), 3.58 (s, 3H), 5.33 (s, 2H), 6.82-6.91 (m, 2H), 6.93 (bs, 1H), 7.22 (t, $J = 8.0$ Hz, 1H), 7.85 (bd, $J = 8.5$ Hz, 2H), 8.12 (bd, $J = 8.5$ Hz, 2H).

20

Example 33

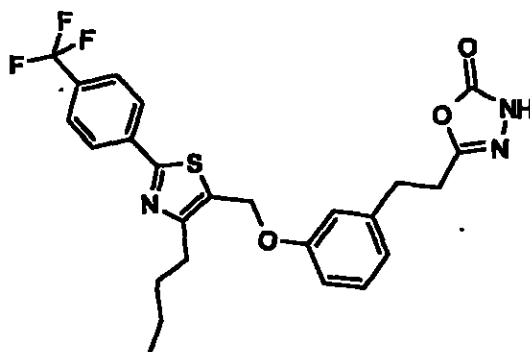


5 Intermediate: 3-(3-(4-butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy)-phenyl)-
propionic acid hydrazide

Follow the procedure of Example 8, but use the compound of Example 32 as the starting material to obtain the title compound.

10 MS (ESI) m/z 478 (M+H); ^1H NMR (DMSO- d_6) δ 0.91 (t, $J = 7.5$ Hz, 3H), 1.36 (m, 2H), 1.68 (m, 2H), 2.33 (m, 2H), 2.80 (m, 4H), 4.14 (bd, $J = 4.0$ Hz, 2H), 5.32 (s, 2H), 6.79-6.92 (m, 3H), 7.21 (t, $J = 7.5$ Hz, 1H), 7.85 (bd, $J = 8.5$ Hz, 2H), 8.12 (bd, $J = 8.5$ Hz, 2H), 8.94 (bm, 1H).

15 Example 34



20 5-(2-(3-(4-butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy)-phenyl)-ethyl)-3H-
[1,3,4]oxadiazol-2-one

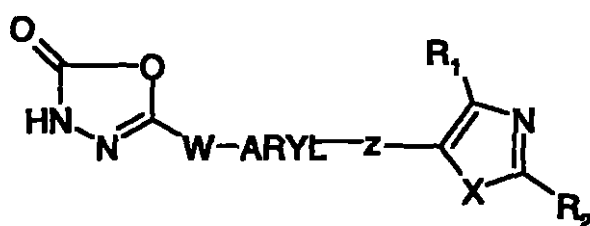
Follow the procedure of Example 10, but use the compound of Example 33 as the starting material to obtain the title compound.

MS (ESI) m/z 504 ($M+H$); ^1H NMR (DMSO- d_6) δ 0.91 (t, $J = 7.5$ Hz, 3H), 1.36 (m, 2H), 1.67 (m, 2H), 2.80 (m, 2H), 2.88 (m, 4H), 5.33 (s, 2H), 6.83-6.93 (m, 2H), 6.97 (bs, 1H), 7.23 (t, $J = 8.0$ Hz, 1H), 7.85 (bd, $J = 8.5$ Hz, 2H), 8.12 (bd, $J = 8.5$ Hz, 2H), 11.5-12.5 (bm, 1H).

CLAIMS

What is claimed is:

1. A compound of formula I:



I

wherein

ARYL is phenyl or pyridinyl, wherein said phenyl or pyridinyl is optionally substituted with one or more substituents selected from the group consisting of halogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, C₁₋₆perfluoroalkyl; C₁₋₆alkylthio, hydroxy, hydroxyC₁₋₆alkyl, C₁₋₆acyloxy, nitro, cyano, C₁₋₆alkylsulfonyl, amino, C₁₋₆alkylamino and C₁₋₆alkoxycarbonyl;

W is a bond or (CH₂)_m, wherein m is an integer from 1 to 4;

Z is -O(CH₂)_n-, -SO₂(CH₂)_n-, -(CH₂)_n-Y-(CH₂)_n-, -(CH₂)_n-CO-, -O(CH₂)_n-CO- or -(CH₂)_n-Y-(CH₂)_n-CO- wherein Y is NR₃, O or S and R₃ is selected from the group consisting of H, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₁₋₆alkylC₃₋₆cycloalkyl and benzyl and n is independently an integer from 1 to 5;

X is NR₃, O or S wherein R₃ is as defined above;

R₁ is H, halogen, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆perfluoroalkyl; hydroxyC₁₋₆alkyl, nitro, cyano, and C₁₋₆alkylamino; and

R₂ is substituted or unsubstituted phenyl, pyridinyl or thienyl wherein the substituents are selected from the group consisting of halogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₁₋₆alkoxy, C₁₋₆perfluoroalkyl, C₁₋₆alkylthio, hydroxy, hydroxyC₁₋₆alkyl, C₁₋₆acyloxy, nitro, cyano, C₁₋₆alkylsulfonyl, amino, C₁₋₆alkylamino and C₁₋₆alkoxycarbonyl; or a stereoisomer, a tautomer or a solvate thereof or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 wherein ARYL is phenyl

3. The compound according to claim 1 wherein ARYL is phenyl; and
R₂ is phenyl.

5

4. The compound according to claim 1 wherein ARYL is phenyl;
Z is -O(CH₂)_n-; and
R₂ is phenyl.

10

5. The compound according to claim 1 wherein ARYL is phenyl;
Z is -O(CH₂)_n-;
X is O or S; and
R₂ is phenyl.

15

6. The compound according to claim 1 wherein ARYL is phenyl;
Z is -O(CH₂)_n-;
X is O or S;
R₁ is C₁₋₆alkyl;
R₂ is phenyl and;
20 W is a bond.

20

7. The compound according to claim 6 wherein X is O.

8. The compound according to claim 6 wherein X is S.

25

9. The compound according to claim 1 wherein ARYL is phenyl;
Z is -(CH₂)_n-Y-(CH₂)_n-; and
R₂ is phenyl.

30

10. The compound according to claim 1 wherein ARYL is phenyl;
Z is -(CH₂)_n-Y-(CH₂)_n-;
X is O or S; and
R₂ is phenyl.

11. The compound according to claim 1 wherein ARYL is phenyl;

Z is $-(CH_2)_x-Y-(CH_2)_x-$;

X is O or S; and

R₁ is C₁₋₆alkyl;

R₂ is phenyl and;

W is a bond.

12. The compound according to claim 11 wherein X is S.

13. The compound of claim 11 wherein Y is O.

14. The compound according to claim 1 wherein ARYL is phenyl;

Z is $-O(CH_2)_n-$;

X is O or S;

R₁ is C₁₋₆alkyl;

R₂ is phenyl and;

W is $(CH_2)_m$, wherein m is an integer from 1 to 4.

15. The compound according to claim 14 wherein X is S.

16. The compound according to claim 1, which is selected from the group consisting of:

5-[4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-phenyl]-3H-

[1,3,4]oxadiazol-2-one 5-[4-(4-methyl-2-*m*-tolyl-oxazol-5-ylmethoxy)-phenyl]-3H-

[1,3,4]oxadiazol-2-one, 5-[4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-yl)-

methoxymethyl]-phenyl]-3H-[1,3,4]oxadiazol-2-one, 5-{3-[4-methyl-2-(4-trifluoromethyl-

phenyl)-thiazol-5-yl)-methoxymethyl]-phenyl}-3H-[1,3,4]oxadiazol-2-one, 5-{4-[4-butyl-2-

(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxy]-2-chloro-phenyl}-3H-[1,3,4]oxadiazol-2-

one, 5-{4-[4-butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethoxymethyl]-2-fluoro-

phenyl}-3H-[1,3,4]oxadiazol-2-one, 5-{4-[4-butyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-

ylmethoxy]-benzyl}-3H-[1,3,4]oxadiazol-2-one, and 5-(2-{3-[4-butyl-2-(4-trifluoromethyl-

phenyl)-thiazol-5-ylmethoxy]-phenyl)-ethyl)-3H-[1,3,4]oxadiazol-2-one.

17. A pharmaceutical composition comprising an effective amount of a compound according to claim 1 and a pharmaceutical acceptable carrier.

18. A method of treating a disease in a mammal wherein the disease is capable of being modulated by PPARdelta ligand binding activity, which comprises administering to said mammal having said disease a therapeutically effective amount of a compound according to claim 1.

19: The method according to claim 11 wherein said disease is a demyelinating disease selected from the group consisting of multiple sclerosis, Charcot-Marie-Tooth disease, Pelizaeus-Merzbacher disease, encephalomyelitis, neuromyelitis optica, adrenoleukodystrophy, Guillian-Barre syndrome and disorders in which myelin forming glial cells are damaged including spinal cord injuries, neuropathies and nerve injury.

20. The method according to claim 12 wherein the demyelinating disease is multiple sclerosis.

21. The method according to claim 11 wherein said disease is selected from the group consisting of obesity, hypertriglyceridemia, hyperlipidemia, hypoalphalipoproteinemia, hypercholesterolemia, dyslipidemia, Syndrome X, Type II diabetes mellitus and complications thereof selected from the group consisting of neuropathy, nephropathy, retinopathy and cataracts, hyperinsulinemia, impaired glucose tolerance, insulin resistance, atherosclerosis, hypertension, coronary heart disease, peripheral vascular disease or congestive heart failure.

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Declarations under Rule 4.17:

- as to the applicant's entitlement to claim the priority of the
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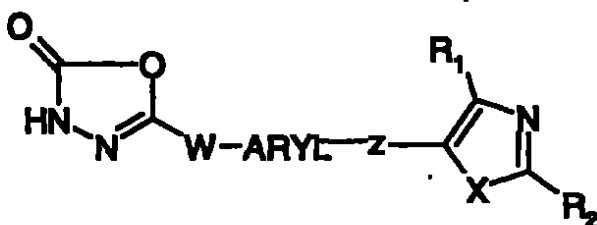
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(54) Title: 1,3,4-OXADIAZOL-2-ONES AS PPAR DELTA MODULATORS



(I)

(57) Abstract: The present invention is directed to 1,
3, 4-oxadiazolones, compounds of formula (I) and their
pharmaceutically acceptable salts stereoisomers, tautomers,
or solvates thereof. Novel compounds include those of
formula (I), in which radicals are as defined herein. The
compounds of this invention are modulators of PPARdelta
and therefore useful as pharmaceutical agents, especially for
the treatment of demyelinating diseases and disorders of fatty
acid metabolism and glucose utilization.

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International Application No
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B. FIELDS SEARCHED

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

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	S. S. KULKARNI ET AL.: "Three-Dimensional Quantitative Structure Activity Relationship (3-D-QSAR) of Antihyperglycemic Agents" BIOORG. MED. CHEM., vol. 7, 1999, pages 1475-1485, XP002345584 figure 1	1-21
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A	WO 01/00603 A (GLAXO GROUP LTD.) 4 January 2001 (2001-01-04) claims 1-50	1-21
	-/-	

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

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

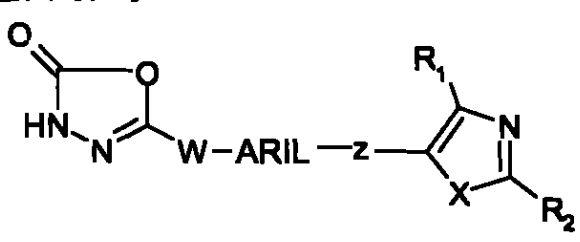
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(54) Título: 1,3,4-oxadiazol-2-onas como moduladores del PPAR DELTA Y LOS USOS DE LAS MISMAS.

(57) Resumen: La presente invención está dirigida a 1,3,4-oxadiazolonas, compuestos de fórmula I y las sales, estereoisómeros, tautómeros, o solvatos farmacéuticamente aceptables de los mismos. Los compuestos novedosos incluye los de fórmula I, en la que los radicales son como se definen en la presente memoria.



I

Los compuestos de esta invención son moduladores del PPAR delta y por lo tanto útiles como agentes farmacéuticos, especialmente para el tratamiento de enfermedades desielinizantes y trastornos del metabolismo de ácidos grasos y de utilización de la glucosa.

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1,3,4-OXADIAZOL-2-ONAS COMO MODULADORES DEL PPAR DELTA Y LOS USOS DE LAS MISMAS

CAMPO DE LA INVENCION

5 Esta invención se refiere a compuestos novedosos y formulaciones farmacéuti-
cas que actúan como ligantes selectivos del receptor de ligandos del PPARdelta, que son
útiles modulando receptores PPARdelta para el tratamiento de enfermedades mediadas
por receptores nucleares de hormonas. Los ligantes selectivos del receptor de ligandos
del PPARdelta de esta invención son útiles como agonistas o antagonistas del receptor
10 PPARdelta.

ANTECEDENTES DE LA INVENCION

Los receptores activados por proliferadores peroxisomales (PPARs por sus si-
glas en inglés) comprenden una subfamilia de la superfamilia de receptores nucleares.
15 Se han identificado y clonado cuatro isoformas estrechamente relacionadas y se cono-
cen comúnmente como PPARalfa, PPARGgamma-1, PPARGgamma-2 y PPARdelta. Cada
subtipo de receptor tiene un dominio de unión a ADN (DBD por sus siglas en inglés)
característico y un dominio de unión a ligando (LBD por sus siglas en inglés), siendo
ambos necesarios para la expresión génica activada por el ligando. Los PPARs se unen
20 como heterodímeros con un receptor del retinoide X. Véase J. Berger y D. E. Miller,
Annu. Rev. Med., 2002, 53, 409-435.

El PPARdelta (también conocido como PPARbeta) se expresa en un amplio in-
tervalo de tejidos de mamíferos, pero se ha elucidado poca información con respecto a
sus funciones biológicas o al conjunto de genes completo regulado por el receptor. Sin
25 embargo, recientemente se ha encontrado que los agonistas pueden ser útiles para tratar
enfermedades tales como la dislipidemia y ciertas enfermedades dermatológicas, mien-
tras que los antagonistas pueden ser útiles para tratar la osteoporosis o el cáncer colorec-
tal (D. Sternbach, en *Annual Reports in Medicinal Chemistry, Volume 38*, A. M. Doherty,
ed., Elsevier Academic Press, 2003 pp. 71-80).

30 El PPARdelta parece expresarse significativamente en el SNC; sin embargo si-
gue sin descubrirse la mayor parte de su función en éste. Sin embargo de singular inte-
rés, es el descubrimiento de que el PPARdelta se expresaba en oligodendrocitos de roe-

dor, las células productoras de lípidos más importantes del SNC (J. Grammman, et al., *J. Neurosci. Res.*, 1998, 51, 563-573). Además, también se encontró que un agonista selectivo del PPAR-delta aumentaba significativamente la expresión génica de mielina oligodendroglial y el diámetro de la vaina de mielina en cultivos de ratón (I. Saluja et al., *Glia*, 2001, 33, 194-204). Por lo tanto, los activadores del PPAR-delta se pueden usar para el tratamiento de enfermedades de desmielinización y dismielinización.

Los estados de desmielinización se ponen de manifiesto por la pérdida de mielina, las múltiples capas densas de lípidos y proteína que cubren muchas fibras nerviosas. Estas capas son proporcionadas por la oligodendroglía en el sistema nervioso central (SNC), y las células Schwann en el sistema nervioso periférico (SNP). En pacientes con estados de desmielinización, la desmielinización puede ser irreversible; normalmente va acompañada o seguida de degeneración axonal, y a menudo de degeneración celular. La desmielinización puede ocurrir como un resultado de daño neuronal o daño a la propia mielina — si se debe a respuestas inmunitarias aberrantes, lesión local, isquemia, trastornos metabólicos, agentes tóxicos, o infecciones virales (Prineas y McDonald, *Demyelinating Diseases. En Greenfield's Neuropatology*, 6ª ed. (Edward Arnold: New York, 1997) 813-811, Beers y Berkow, eds., *The Merck Manual of Diagnosis y Therapi*, 17ª ed. (Whitehouse Station, N.J.: Merck Research Laboratories, 1999) 1299, 1437, 1473-76, 1483).

La desmielinización central (desmielinización del SNC) se produce en diferentes enfermedades, a menudo de etiología indeterminada, que se han conocido como las enfermedades de desmielinización primarias. De éstas, la esclerosis múltiple (EM) es la más extendida. Otras enfermedades desmielinizantes primarias incluyen adrenoleucodistrofia (ALD), adrenomieloneuropatía, mielopatía vacuolar asociada al SIDA, mielopatía asociada a HTLV, atrofia óptica hereditaria de Leber, leucoencefalopatía multifocal progresiva (LMP), panencefalitis esclerosante subaguda, síndrome de Guillain-Barre y paraparesia espástica tropical. Además, hay enfermedades agudas en las que se puede producir la desmielinización en el SNC, por ejemplo, en la encefalomiелitis diseminada aguda (EMDA) y encefalitis vírica aguda. Además, la miелitis transversa aguda, que es un síndrome en el que una transección aguda de la médula espinal de causa desconocida afecta tanto a la materia gris como a la blanca en uno o más segmentos torácicos adyacentes, puede dar como resultado la desmielinización. También, los trastornos en los

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que las células gliales formadoras de mielina son dañadas, incluyendo lesiones de la médula espinal, neuropatías y lesión nerviosa.

Los moduladores selectivos del PPARdelta también pueden ser útiles para tratar o prevenir otros estados patológicos véase, por ejemplo, Joel Berger et al., Annu. Rev. Med. 2002, 53, 409 – 435; Timoty Wilson et al. J. Med. Chem., 2000, Vol. 43, nº 4, 527-550; Steven Kliewer et al., Recent Prog. Horm. Res. 2001; 56: 239-63; Jean-Charles Fruchart, Bart Staels y Patrick Duriez: PPARS, Metabolic Disease y Arteriosclerosis, Pharmacological Research, Vol. 44, nº 5, 345-52; 2001; Sander Kersten, Beatrice Desvergne y Walter Wahli: Roles of PPARs in health y disease, Nature, vol 405, 25 de mayo de 2000; 421-4; Inés Pineda Torra, Giulia Chinetti, Caroline Duval, Jean-Charles Fruchart y Bart Staels: Peroxisome proliferator-activated receptors: from transcriptional control to clinical practice, Curr. Opin. Lipidol. 12: 2001, 245-254).

Los compuestos que actúan como moduladores PPARdelta pueden ser particularmente adecuados para el tratamiento y/o prevención de trastornos del metabolismo de ácidos grasos y trastornos de la utilización de glucosa en los que está implicada la insulinoresistencia.

La Diabetes mellitus, especialmente la diabetes de tipo 2, incluyendo la prevención de las secuelas asociadas con la misma. Son aspectos particulares relacionados con ésta: hiperglucemia, mejora en insulinoresistencia, mejora en tolerancia a la glucosa, protección de las células pancreáticas β , prevención de trastornos macro- y microvasculares.

Las dislipidemias y sus secuelas tales como, por ejemplo, aterosclerosis, enfermedad coronaria cardiaca, trastornos cerebrovasculares etc, especialmente los (pero no restringidos a ellos) que se caracterizan por uno o más de los factores siguientes: concentraciones plasmáticas de triglicéridos altas, concentraciones plasmáticas de triglicéridos posprandiales altas, concentraciones de colesterol transportado por las HDL bajas, concentraciones de lipoproteína ApoA bajas, concentraciones de colesterol transportado por las LDL altas, partículas densas de colesterol transportado por las LDL pequeñas, concentraciones de lipoproteína ApoB altas.

Otras diversas enfermedades que se pueden asociar con el síndrome metabólico, tales como: obesidad (exceso de peso), incluyendo obesidad central, trombosis, estados hipercoagulables y protrombóticos (arteriales y venosos), presión sanguínea alta, insufi-

ciencia cardiaca tal como, por ejemplo (pero no restringido a esto), después de infarto de miocardio, enfermedad cardiaca hipertensiva o cardiomiopatía.

Otros trastornos o enfermedades en las que por ejemplo pueden estar implicadas reacciones inflamatorias o diferenciación celular, son: aterosclerosis tal como, por ejemplo (pero no restringido a esto), esclerosis coronaria que incluye angina de pecho o infarto de miocardio, apoplejía, reestenosis o reoclusión vasculares, enfermedades inflamatorias crónicas del intestino, tales como, por ejemplo, enfermedad de Crohn y colitis ulcerosa, pancreatitis, otros estados inflamatorios, retinopatía, tumores de adipocitos, carcinomas lipomatosos tales como, por ejemplo, liposarcomas, tumores sólidos y neoplasmas tales como, por ejemplo (pero no restringidos a estos), carcinomas del tubo gastrointestinal, del hígado, del tubo biliar y del páncreas, tumores endocrinos, carcinomas de los pulmones, de los riñones y del tubo urinario, del tubo genital, carcinomas de próstata etc., trastornos mieloproliferativos agudos y crónicos y angiogénesis de linfomas, trastornos neurodegenerativos, enfermedad de Alzheimer, enfermedad de Parkinson, dermatosis eritematoescamosas tales como, por ejemplo, psoriasis, acné vulgar.

Otros trastornos de la piel y enfermedades dermatológicas moduladas por el PPARdelta:

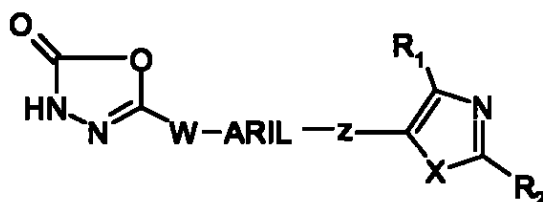
- eczemas y neurodermitis, dermatitis tales como, por ejemplo, dermatitis seborreica o fotodermatitis, queratitis y queratosis tales como, por ejemplo, queratosis seborreica, queratosis senil, queratosis actínica, queratosis fotoinducida o queloides de queratosis folicular y profilaxis de queloides, verrugas, que incluyen condilomas o condilomas acuminados, infecciones por virus de papiloma humano (VPH) tales como, por ejemplo, papilomas venéreos, verrugas virales tales como, por ejemplo, molusco contagioso (*molluscum contagiosum*), dermatosis leucoplasia papular tal como, por ejemplo, Liquen plano, cáncer de piel tal como, por ejemplo, carcinomas de células basales, melanomas o linfomas cutáneos de células T, tumores epidérmicos benignos localizados tales como, por ejemplo, queratoderma, nevo epidérmico y sabañones.

Otras enfermedades diversas moduladas potencialmente por el PPARdelta que incluyen síndrome X, síndrome de ovario poliquístico (PCOS), asma osteoartritis, lupus eritematoso (LE) o trastornos reumáticos inflamatorios tales como, por ejemplo, artritis reumatoide, vasculitis, deterioro (caquexia), síndrome de isquemia/reperfusión de gota y síndrome de dificultad respiratoria aguda (SDRA).

COMPENDIO DE LA INVENCION

La presente invención está dirigida a compuestos de fórmula I.

5



I

en la que

- 10 **ARILO** es fenilo o piridinilo, en el que dicho fenilo o piridinilo está opcionalmente sustituido con uno o más sustituyentes seleccionados del grupo que consiste en halógeno, alquiloC₁₋₆, alqueniloC₂₋₆, alcoxiC₁₋₆, perfluoroalquiloC₁₋₆; alquiltioC₁₋₆, hidroxil, hidroxialquiloC₁₋₆, aciloxiC₁₋₄, nitro, ciano, alquilsulfoniloC₁₋₆, amino, alquilaminoC₁₋₆ y alcoxiC₁₋₆carbonilo;
- 15 **W** es un enlace o (CH₂)_m, en el que m es un número entero de 1 a 4;
Z es -O(CH₂)_n-, -SO₂(CH₂)_n-, -(CH₂)_n-Y-(CH₂)_n-, -(CH₂)_n-CO-, -O(CH₂)_n-CO- o -(CH₂)_n-Y-(CH₂)_n-CO- en el que Y es NR₃, O o S y R₃ se seleccionan del grupo que consiste en H, alquiloC₁₋₆, cicloalquiloC₃₋₈, alquilC₁₋₆cicloalquiloC₃₋₈ y bencilo y n es independientemente un número entero de 1 a 5;
- 20 **X** es NR₃, O o S en el que R₃ es como se define más arriba;
R₁ es H, halógeno, alquiloC₁₋₆, alcoxiC₁₋₆, perfluoroalquiloC₁₋₆; hidroxialquiloC₁₋₆, nitro, ciano, y alquilC₁₋₆amino; y
R₂ es fenilo, piridinilo o tienilo sustituidos o no sustituidos en los que los sustituyentes se seleccionan del grupo que consiste en halógeno, alquiloC₁₋₆, alqueniloC₂₋₆, alcoxiC₁₋₆, perfluoroalquiloC₁₋₆, alquiltioC₁₋₆, hidroxil, hidroxialquiloC₁₋₆, aciloxiC₁₋₄, nitro, ciano, alquilC₁₋₆sulfonilo, amino, alquilC₁₋₆amino y alcoxiC₁₋₆carbonilo; o un estereoisómero, un tautómero o un solvato del mismo o una sal farmacéuticamente aceptable del mismo.
- 25

La presente invención también está dirigida a las composiciones farmacéuticas de fórmula I, y a los métodos de usar dichos compuestos y composiciones para modular

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el PPARdelta en sujetos que necesitan de tal modulación administrando un compuesto que preferentemente modulan la actividad del PPARdelta. Los presentes compuestos poseen actividad moduladora del PPARdelta útil, y se espera que sean útiles en el tratamiento o profilaxis de una enfermedad o dolencia en la que dicha enfermedad es capaz de tratarse por modulación de la actividad de unión de ligando del PPARdelta, administrando al paciente una cantidad terapéuticamente eficaz del compuesto de fórmula I.

DESCRIPCIÓN DETALLADA DE LA INVENCION

Los términos y expresiones, tal como se usan en esta memoria, tienen los siguientes significados:

Como se utiliza en la presente memoria, la expresión "alquilo C₁₋₆" incluye grupos metilo y etilo, y grupos propilo, butilo, pentilo y hexilo de cadena lineal o ramificada. Los grupos alquilo concretos son metilo, etilo, n-propilo, isopropilo y terc-butilo. Las expresiones derivadas tales como "alcoxiC₁₋₆", "alcoxiC₁₋₆alquiloC₁₋₆", "hidroxialquiloC₁₋₆", "alquilC₁₋₆carbonilo", "alcoxiC₁₋₆carbonilalquiloC₁₋₆", "alcoxiC₁₋₆carbonilo", "aminoalquiloC₁₋₆", "alquilC₁₋₆carbamoilalquiloC₁₋₆", "dialquilC₁₋₆carbamoilalquiloC₁₋₆" "mono- o di-alquilC₁₋₆aminoalquiloC₁₋₆", aminoalquilC₁₋₆carbonilo", "difenilalquiloC₁₋₆", "arilalquiloC₁₋₆", "arilcarbonilalquiloC₁₋₆" y "ariloxialquiloC₁₋₆" se deben interpretar en consecuencia.

Tal como se utiliza en la presente, la expresión "alquenilo C₂₋₆" incluye grupos etenilo y propenilo, butenilo, pentenilo y hexenilo de cadena lineal o ramificada. De forma similar, la expresión "alquinilo C₂₋₆" incluye grupos etinilo y propinilo, y butinilo, pentinilo y hexinilo de cadena lineal o ramificada.

Como se utiliza en la presente memoria "arilo" representa un sistema de anillo aromático carbocíclico tal como fenilo, bifenilo, naftilo, antracenilo, fenantrenilo, fluorenilo, indenilo, pentalenilo, azulenilo, bifenilenilo y similares. El arilo también tiene la finalidad de incluir los derivados parcialmente hidrogenados de los sistemas aromáticos carbocíclicos enumerados más arriba. Ejemplos no limitantes de tales derivados parcialmente hidrogenados son 1,2,3,4-tetrahidronaftilo, 1,4-dihidronaftilo y similares.

Como se utiliza en la presente memoria "ariloxi" representa un grupo -O-aril en el que arilo es como se define más arriba.

Como se utiliza en la presente memoria "heteroarilo" (por si mismo o en cual-

5 quier combinación, tal como "heteroariloxi", o "heteroarilo alquilo")— un sistema de anillo aromático de 5-10 miembros en el que uno o más anillos contienen uno o más heteroátomos seleccionados del grupo que consiste en N, O o S, tal como, pero no limitado a, pirrol, pirazol, furano, tiofeno, quinolina, isoquinolina, quinazolinilo, piridina, pirimidina, oxazol, tiazol, tiadiazol, tetrazol, triazol, imidazol, o bencimidazol.

10 Como se utiliza en la presente memoria "heterocíclico o heterociclilo" (por si mismos o en cualquier combinación, tal como "heterociclilalquilo")— un sistema de anillo de 4-10 miembros saturado o parcialmente insaturado en el que uno o más anillos contienen uno o más heteroátomos seleccionados del grupo que consiste en N, O, o S; tales como, pero no limitados a, pirrolidina, piperidina, piperazina, morfolina, tetrahidro pirano, o imidazolidina.

15 Tal como se utiliza en la presente, la expresión "perfluoroalquilo C₁₋₆" significa que todos los átomos de hidrógeno en dicho grupo alquilo se sustituyen por átomos de flúor. Los ejemplos ilustrativos incluyen grupos trifluorometilo y pentafluoroetilo, y heptafluoropropilo, nonafluorobutilo, undecafluoropentilo y tridecafluorohexilo de cadena lineal o ramificada. La expresión derivada "perfluoroalcoxi C₁₋₆" debe interpretarse en consecuencia.

Tal como se usa en esta memoria, la expresión "cicloalquilo C₃₋₈" significa ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo y ciclooctilo.

20 Tal como se usa en esta memoria, la expresión "cicloalquil(C₃₋₈)-alquilo(C₁₋₆)" significa que el cicloalquilo C₃₋₈ como se define en esta memoria, además está unido al alquilo C₁₋₆ como se define en esta memoria. Los ejemplos representativos incluyen ciclopropilmetilo, 1-ciclobutiletilo, 2-ciclopentilpropilo, ciclohexilmetilo, 2-cicloheptiletilo y 2-ciclooctilbutilo y similares.

25 Tal como se usa en esta memoria "halógeno" significa cloro, flúor, bromo y yodo.

30 Como se utiliza en la presente memoria "alquilC₁₋₆sulfonilo" en el presente contexto designa un grupo --S(=O)₂alquiloC₁₋₆ en el que alquiloC₁₋₆ es como se define más arriba. Los ejemplos representativos incluyen, pero no se limitan a, metilsulfonilo, etilsulfonilo, n-propilsulfonilo, isopropilsulfonilo, butilsulfonilo, iso-butilsulfonilo, sec-butilsulfonilo, terc-butilsulfonilo, n-pentilsulfonilo, isopentilsulfonilo, neopentilsulfonilo, terc-pentilsulfonilo, n-hexilsulfonilo, isohexilsulfonilo y similares.

Como se utiliza en la presente memoria "arilsulfonilo" representa un grupo --S(=O)₂aril en el que arilo es como se define más arriba.

Como se utiliza en la presente memoria "heteroarilsulfonilo" representa un grupo --S(=O)₂heteroaril en el que heteroarilo es como se define más arriba.

- 5 La expresión "estereoisómero" es un término general utilizado para todos los isómeros de las moléculas individuales que solamente difieren en la orientación de sus átomos en el espacio. De forma típica, incluye los isómeros de imagen especular que normalmente se forman debido al menos a un centro asimétrico (enantiómeros). Cuando los compuestos de acuerdo con la invención tienen dos o más centros asimétricos, pueden existir
10 adicionalmente como diastereoisómeros, y también algunas moléculas individuales pueden existir como isómeros geométricos (cis/trans). Hay que entender que todos dichos isómeros y sus mezclas en cualquier proporción están englobadas dentro del alcance de la presente invención.

- "Sustituido" significa sustituido por 1 a 2 sustituyentes independientemente seleccionados del grupo que consiste en alquilo C₁₋₆, perfluoroalquilo C₁₋₆, hidroxilo, -CO₂H, un éster, una amida, alcoxi C₁₋₆, perfluoroalcoxi C₁₋₆, -NH₂, Cl, Br, I, F, -NH-alquil inferior, y -N(alquil inferior)₂.

- Los compuestos y sales de la presente invención pueden existir en varias formas tautómeras, que incluyen la forma enólica e imínica, y la forma ceto y enamina y sus
20 isómeros geométricos y sus mezclas. Todas de tales formas tautómeras están incluidas dentro del alcance de la presente invención. Los tautómeros existen como mezclas de un conjunto tautómero en disolución. En forma sólida, normalmente predomina un tautómero. Aunque se puede describir un tautómero, la presente invención incluye todos los tautómeros de los presentes compuestos.

- 25 Como se utiliza en la presente memoria el término "modulador" se refiere a un compuesto químico con capacidad para o mejorar (por ejemplo, actividad "agonista") o inhibir (por ejemplo, actividad "antagonista") una propiedad funcional de actividad biológica o proceso (por ejemplo, actividad enzimática o unión al receptor); tal mejora o inhibición puede depender de la ocurrencia de un evento específico, tal como la activación o represión de una vía de la transducción de señales y/o se puede manifestar sola-
30 mente en tipos celulares particulares y puede dar como resultado un cambio biológico medible.

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Tal y como se utiliza en la presente memoria, "paciente" significa un animal de sangre caliente, tal como por ejemplo, ratas, ratones, perros, gatos, cobayas, y primates tales como los seres humanos.

5 Tal como se usa en esta memoria, la expresión "vehículo farmacéuticamente aceptable" significa un disolvente, dispersante, excipiente, adyuvante u otro material no tóxico, que se mezcla con el compuesto de la presente invención, con el fin de permitir la formación de una composición farmacéutica, es decir, una forma de dosificación que se pueda administrar al paciente. Un ejemplo de dicho vehículo es un aceite farmacéu-

10 El término "sales farmacéuticamente aceptables", tal como se usa en la presente memoria, significa que las sales de los compuestos de la presente invención pueden usarse en preparaciones medicinales. Sin embargo, pueden resultar útiles otras sales en la preparación de los compuestos acordes con la invención, o de sus sales farmacéu-
15 ticamente aceptables. Las sales farmacéuticamente aceptables de los compuestos de esta invención incluyen sales de adición de ácido que se pueden formar, por ejemplo, mez-
clando una solución del compuesto de acuerdo con la invención, con una solución de un ácido farmacéuticamente aceptable tal como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido metanosulfónico, ácido 2-hidroxietanosulfónico, ácido p-
20 toluenosulfónico, ácido fumárico, ácido maleico, ácido hidroximaleico, ácido málico, ácido ascórbico, ácido succínico, ácido glutárico, ácido acético, ácido salicílico, ácido cinámico, ácido 2-fenoxiacético, ácido hidroxibenzoico, ácido fenilacético, ácido ben-
zoico, ácido oxálico, ácido cítrico, ácido tartárico, ácido glicólico, ácido láctico, ácido pirúvico, ácido malónico, ácido carbónico o ácido fosfórico. También pueden formarse sales de metales ácidas, como monohidrógeno-ortofosfato de sodio e hidrógeno-sulfato
25 de potasio. Además, las sales así formadas pueden estar presentes como sales de mono o di-ácido y pueden existir en forma hidratada o pueden ser sustancialmente anhidras. Además, cuando los compuestos de la invención tienen un resto ácido, sus sales farma-
céuticamente aceptables adecuadas pueden incluir sales de metales alcalinos, por ejem-
plo sales de sodio o de potasio; sales de metal alcalinotérreo, por ejemplo, sales de cal-
30 cio o magnesio; y sales formadas con ligandos orgánicos adecuados, por ejemplo, sales de amonio cuaternarias.

La terminología "cantidad terapéuticamente eficaz" como se utiliza en la presen-

te memoria significa una cantidad del compuesto que es eficaz en el tratamiento del trastorno o dolencia mencionada.

La invención también proporciona composiciones farmacéuticas que comprenden uno o más de los compuestos de acuerdo con esta invención, junto con un vehículo farmacéuticamente aceptable. Preferiblemente, estas composiciones están en formas de dosificaciones unitarias tales como comprimidos, píldoras, cápsulas, polvos, gránulos, soluciones o suspensiones parenterales estériles, aerosoles o pulverizadores líquidos dosificados, gotas, ampollas, dispositivos de autoinyección o supositorios; para la administración oral, parenteral, intranasal, sublingual o rectal, o para la administración por inhalación o insuflación. Alternativamente, las composiciones pueden presentarse en una forma adecuada para la administración una vez semanal o una vez mensual; por ejemplo, una sal insoluble del compuesto activo, como la sal decanoato, puede adaptarse para proporcionar una preparación de depósito para la inyección intramuscular. Puede contemplarse un polímero erosionable que contiene el ingrediente activo. Para preparar composiciones sólidas como comprimidos, el ingrediente activo principal se mezcla con un vehículo farmacéutico, por ejemplo ingredientes convencionales para formar comprimidos, tal como almidón de maíz, lactosa, sacarosa, sorbitol, talco, ácido esteárico, estearato de magnesio, fosfato de dicalcio o gomas, y otros diluyentes farmacéuticos, por ejemplo agua, para formar una composición de preformulación sólida que contiene una mezcla homogénea de un compuesto de la presente invención, o su sal farmacéuticamente aceptable. Cuando se indica que estas composiciones de preformulación son homogéneas, significa que el ingrediente activo está disperso de modo uniforme a través de la composición, de forma que la composición puede subdividirse con facilidad en formas de dosificación unitarias igualmente eficaces, como comprimidos, píldoras y cápsulas. Esta composición de preformulación sólida se subdivide entonces en formas de dosificación unitarias del tipo descrito anteriormente, que contienen desde 0,1 a aproximadamente 500 mg del ingrediente activo de la presente invención. Las formas de dosificación unitaria aromatizadas contienen desde 1 a 100 mg, por ejemplo 1, 2, 5, 10, 25, 50 ó 100 mg, del ingrediente activo. Los comprimidos o píldoras de la nueva composición pueden revestirse o componerse de otro modo para proporcionar una forma de dosificación que permita la ventaja de una acción prolongada. Por ejemplo, el comprimido o píldora puede comprender un componente de dosificación interno y uno

de dosificación externo, estando éste último en forma de una envuelta sobre el primero. Los dos componentes se pueden separar por una capa entérica, que sirve para resistir la disgregación en el estómago y permite al componente interno pasar intacto en el duodeno o retrasarse en la liberación. Puede utilizarse una diversidad de materiales para estas
5 capas o revestimientos entéricos, incluyendo dichos materiales una serie de ácidos poliméricos y mezclas de ácidos poliméricos con materiales tales como goma de laca, alcohol cetílico y acetato de celulosa.

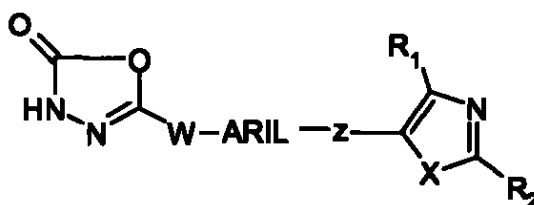
Las formas líquidas en las que las nuevas composiciones de esta memoria invención pueden incorporarse para su administración por vía oral o mediante inyección in-
10 cluyen disoluciones acuosas, jarabes aromatizados de forma apropiada, suspensiones acuosas u oleosas, y emulsiones aromatizadas con aceites comestibles tales como aceite de semilla de algodón, aceite de sésamo, aceite de coco o aceite de cacahuete, así como elixires y vehículos farmacéuticos similares. Los agentes dispersantes o de suspensión adecuados para las suspensiones acuosas incluyen gomas sintéticas y naturales como
15 tragacanto, goma arábiga, alginato, dextrano, carboximetilcelulosa de sodio, metilcelulosa, polivinilpirrolidona o gelatina.

En el tratamiento de los diversos estados patológicos como se describe en la presente memoria, un nivel de dosificación adecuado es desde aproximadamente 0,01 a 250 mg/kg diarios, preferiblemente desde aproximadamente 0,05 a 100 mg/kg diarios, y en
20 especial desde aproximadamente 0,05 a 20 mg/kg diarios. Los compuestos pueden administrarse en un régimen de 1 a 4 veces diarias.

Tal como se utilizan en los ejemplos y preparaciones que aparecen a continuación, los términos que se emplean en éstos tienen los significados indicados: "kg" se refiere a kilogramos, "g" se refiere a gramos, "mg" se refiere a miligramos, "µg" se refiere
25 a microgramos, "pg" se refiere a picogramos, "mol" se refiere a moles, "nmol" se refiere a milimoles, "nmole" se refiere a nanomoles, "L" se refiere a litros, "mL" o "ml" se refiere a mililitros, "µL" se refiere a microlitros, "°C" se refiere a grados Celsius, "R_f" se refiere a factor de retención, "pf" o "p.f." se refiere a punto de fusión, "desc" se refiere a descomposición, "pe" o "p.e." se refiere a punto de ebullición, "mm de Hg" se refiere
30 a presión en milímetros de mercurio, "cm" se refiere a centímetros, "nm" se refiere a nanómetros, "[α]²⁰_D" se refiere a rotación específica de la línea D del sodio a 20°C obtenida en una cubeta de 1 decímetro, "c" se refiere a concentración en g/mL, "THF" se

refiere a tetrahidrofurano, "DMF" se refiere a dimetilformamida, "NMP" se refiere a 1-metil-2-pirrolidinona, "salmuera" se refiere a una disolución acuosa saturada de cloruro sódico, "M" se refiere a molar, "mM" se refiere a milimolar, "μM" se refiere a micromolar, "nM" se refiere a nanomolar, "TLC" se refiere a cromatografía en capa fina, "HPLC" se refiere a cromatografía líquida de alta eficacia, "HRMS" se refiere a espectro de masas de alta resolución, "CIMS" se refiere a espectrometría de masas de ionización química, "ESI" se refiere a espectrometría de masas de ionización por electropulverización, "t_R" se refiere a tiempo de retención, "lb" se refiere a libras, "gal" se refiere a galones, "L.O.D." se refiere a pérdida por desecación, "μCi" se refiere a microcurios, "i.p." se refiere a intraperitonealmente, "i.v." se refiere a intravenosamente.

En un aspecto de esta invención se describen compuestos novedosos que tienen la estructura general mostrada en la fórmula I:



I

en la que

ARIL es fenilo o piridinilo, en el que dicho fenilo o piridinilo está opcionalmente sustituido con uno o más sustituyentes seleccionados del grupo que consiste en halógeno, alquiloC₁₋₆, alqueniloC₂₋₆, alcoxiC₁₋₆, perfluoroalquiloC₁₋₆; alquiltioC₁₋₆, hidroxilo, hidroxialquiloC₁₋₆, aciloxiC₁₋₄, nitro, ciano, alquilsulfoniloC₁₋₆, amino, alquilaminoC₁₋₆ y alcoxiC₁₋₆carbonilo;

W es un enlace o (CH₂)_m, en el que m es un número entero de 1 a 4;

Z es -O(CH₂)_n-, -SO₂(CH₂)_n-, -(CH₂)_n-Y-(CH₂)_n-, -(CH₂)_n-CO-, -O(CH₂)_n-CO-

o -(CH₂)_n-Y-(CH₂)_n-CO- en el que Y es NR₃, O o S y R₃ se seleccionan del grupo que consiste en H, alquiloC₁₋₆, cicloalquiloC₃₋₆, alquilC₁₋₆cicloalquiloC₃₋₆ y bencilo y n es independientemente un número entero de 1 a 5;

X es NR₃, O o S en el que R₃ es como se define más arriba;

R₁ es H, halógeno, alquiloC₁₋₆, alcoxiC₁₋₆, perfluoroalquiloC₁₋₆; hidroxialquiloC₁₋₆, nitro, ciano, y alquilC₁₋₆amino; y

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R₂ es fenilo, piridinilo o tienilo sustituidos o no sustituidos en los que los sustituyentes se seleccionan del grupo que consiste en halógeno, alquiloC₁₋₆, alqueniloC₂₋₆, alcoxiC₁₋₆, perfluoroalquiloC₁₋₆, alquiltioC₁₋₆, hidroxil, hidroxialquiloC₁₋₆, aciloxiC₁₋₄, nitro, ciano, alquilC₁₋₆sulfonilo, amino, alquilC₁₋₆amino y alcoxiC₁₋₆carbonilo; o un estereoisómero, un tautómero o un solvato del mismo o una sal farmacéuticamente aceptable del mismo.

En un aspecto adicional de esta realización, se describe un compuesto en el que **ARILO** es fenilo.

Los compuestos de ejemplo de esta realización se seleccionan del grupo que consiste en: 5-{4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-3H-[1,3,4]oxadiazol-2-ona, 5-[4-(4-metil-2-*m*-tolil-oxazol-5-ilmetoxi)-fenil]-3H-[1,3,4]oxadiazol-2-ona, 5-{4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metoximetil}-fenil}-3H-[1,3,4]oxadiazol-2-ona, 5-{3-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metoximetil}-fenil}-3H-[1,3,4]oxadiazol-2-ona, 5-{4-[4-butil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-cloro-fenil}-3H-[1,3,4]oxadiazol-2-ona, 5-{4-[4-butil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoximetil]-2-fluoro-fenil}-3H-[1,3,4]oxadiazol-2-ona, 5-{4-[4-butil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-bencil}-3H-[1,3,4]oxadiazol-2-ona, y 5-(2-{3-[4-butil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-etil)-3H-[1,3,4]oxadiazol-2-ona.

En otro aspecto de esta realización, se describe un compuesto en el que **ARILO** es fenilo y **R₂** es fenilo.

En un aspecto adicional de esta realización, se describe un compuesto en el que **ARILO** es fenilo, **Z** es -O(CH₂)_n- y **R₂** es fenilo.

Aún en otro aspecto de esta realización, se describe un compuesto en el que **ARILO** es fenilo, **Z** es -O(CH₂)_n-, **X** es O o S y **R₂** es fenilo.

En otro aspecto de esta realización, se describe un compuesto en el que **ARILO** es fenilo, **Z** es -O(CH₂)_n-, **X** es O o S, **R₁** es alquiloC₁₋₆ y **R₂** es fenilo y **W** es un enlace.

En un aspecto adicional de esta realización, se describe un compuesto en el que **X** es O.

Aún en otro aspecto de esta realización, se describe un compuesto en el que **X** es S.

En un aspecto adicional de esta realización, se describe un compuesto en el que

ARILO es fenilo, Z es $-(CH_2)_n-Y-(CH_2)_n-$ y R_2 es fenilo.

Aún en otro aspecto de esta realización, se describe un compuesto en el que ARILO es fenilo, Z es $-(CH_2)_n-Y-(CH_2)_n-$, X es O o S y R_2 es fenilo.

En otro aspecto de esta realización, se describe un compuesto en el que ARILO es fenilo, Z es $-(CH_2)_n-Y-(CH_2)_n-$, X es O o S, R_1 es alquilo C_{1-6} y R_2 es fenilo y W es un enlace.

Aún en otro aspecto de esta realización, se describe un compuesto en el que X es S.

En otro aspecto de esta realización, se describe un compuesto en el que Y es O.

En un aspecto adicional de esta realización, se describe un compuesto en el que ARILO es fenilo, Z es $-O(CH_2)_n-$ y R_2 es fenilo.

Aún en otro aspecto de esta realización, se describe un compuesto en el que ARILO es fenilo, Z es $-O(CH_2)_n-$, X es O o S y R_2 es fenilo, R_1 es alquilo C_{1-6} y R_2 es fenilo y W es $(CH_2)_m$ en el que m es un número entero de 1 a 4.

Aún en otro aspecto de esta realización, se describe un compuesto en el que X es S.

En otra realización de la presente invención, se describe una composición farmacéutica que comprende una cantidad eficaz de un compuesto de fórmula I y un vehículo farmacéutico aceptable.

En otra realización de la presente invención, se describe el método de tratar una enfermedad en un mamífero en el que la enfermedad es capaz de ser, modulada por la actividad de unión del ligando del PPARdelta, que comprende administrar a dicho mamífero que tiene dicha enfermedad una cantidad terapéuticamente eficaz de un compuesto de fórmula I.

En un aspecto adicional de esta realización, se describe un método en el que dicha enfermedad es una enfermedad desmielinizante seleccionada del grupo que consiste en esclerosis múltiple, enfermedad de Charcot-Marie-Toot, enfermedad de Pelizaeus-Merzbacher, encefalomielitis, neuromielitis óptica, adenoleucodistrofia, síndrome de Guillian-Barre y trastornos en los que se dañan neuroglíocitos formadores de mielina que incluyen lesiones de médula espinal, neuropatías y lesión nerviosa.

En otro aspecto de esta realización, se describe un método en el que la enfermedad desmielinizante es la esclerosis múltiple.

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Aún en otro aspecto de esta invención se describe un método en el que dicha enfermedad se selecciona del grupo que consiste en obesidad, hipertrigliceridemia, hiperlipidemia, hipoalfalipoproteinemia, hipercolesterolemia, dislipidemia, Síndrome X, diabetes mellitus de Tipo II y complicaciones de las mismas seleccionadas del grupo que
5 consiste en neuropatía, nefropatía, retinopatía y cataratas, hiperinsulinemia, disminución de la tolerancia a la glucosa, insulinoresistencia, aterosclerosis, hipertensión, enfermedad coronaria cardíaca, enfermedad vascular periférica o insuficiencia cardíaca congestiva.

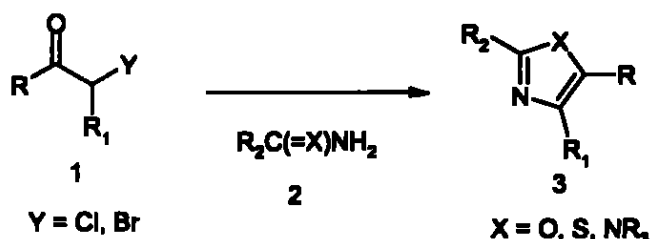
Los compuestos descritos en la presente memoria se pueden sintetizar según los
10 procedimientos de los Esquemas siguientes, en los que los sustituyentes X, y R son como se definen para la fórmula (I), más arriba a menos que se indique otra cosa. Entendiéndose que ciertos productos de partida en los esquemas sintéticos estarían comercialmente disponibles o cuya síntesis sería obvia para los expertos en la técnica.

Si es necesario, en los esquemas sintéticos siguientes, los grupos funcionales re-
15 activos presentes en los compuestos descritos en esta invención pueden estar protegidos por grupos protectores adecuados. El grupo protector se puede eliminar en una etapa posterior de la síntesis. Se pueden encontrar procedimientos para proteger grupos funcionales reactivos y su posterior eliminación en T. W. Greene y P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley y Sons, 1991.

20 El Esquema A muestra la síntesis del imidazol, oxazol o tiazol apropiados, intermedios para los compuestos de fórmula I en la que X es O, S, NR₃. Los heterociclos se pueden preparar utilizando métodos conocidos en la bibliografía química (para una revisión véase Katritzky, A.R.; Rees, C.W. Eds. *Comprehensive Heterocyclic Chemistry*, Vol. 5; Pergamon Press (1984); Katritzky, A.R.; Rees, C.W.; Scriven, E.F.V. Eds.
25 *Comprehensive Heterocyclic Chemistry II*; Vols 3 y 4, Pergamon Press (1996)). Específicamente, dichos oxazoles, imidazoles y tiazoles se pueden preparar por fusión de una α halo-cetona 1 apropiada, respectivamente, con una amida, amidina o una tioamida (fórmula general 2), a temperaturas que se extienden desde aproximadamente 40°C a 150°C para dar los heterociclos intermedios 3.

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Esquema A



5 En el Esquema B se muestra la síntesis general de compuestos de fórmula I en la que Z es $-O(CH_2)_n-$. Por consiguiente, en la Etapa B1 se reduce el éster de ácido carboxílico 4 apropiadamente sustituido, que se puede sintetizar como se ilustra en el Esquema A, al alcohol 5 por métodos que son bien conocidos en la técnica. Por ejemplo, la reducción se puede efectuar por hidruros de aluminio tales como hidruros de litio y aluminio o hidruro de diisobutilaluminio en un disolvente inerte. En la Etapa B2, el grupo funcional alcohol en el compuesto 5, se convierte en un grupo saliente para dar el compuesto 6, en el que Lg es un grupo saliente tal como halógeno, o ésteres de sulfonato, por ejemplo mesilatos o tosilatos. La conversión en el grupo saliente se puede conseguir por reacción del alcohol con reactivos como la N-bromosuccinimida en presencia de trietilfosfina para producir un compuesto en el que el grupo saliente es bromuro, o reacción con cloruro de tionilo para dar un compuesto en el que el grupo saliente es cloruro. Si se desea un éster de sulfonato, la reacción del compuesto 5 con un cloruro de sulfonilo apropiado en presencia de una base adecuada produciría el éster de sulfonato deseado. Por ejemplo, la reacción del compuesto 5 con cloruro de metanosulfonilo en presencia de una base orgánica tal como trietilamina o piridina en un disolvente inerte daría el compuesto 6 en el que el grupo saliente es OSO_2CH_3 .

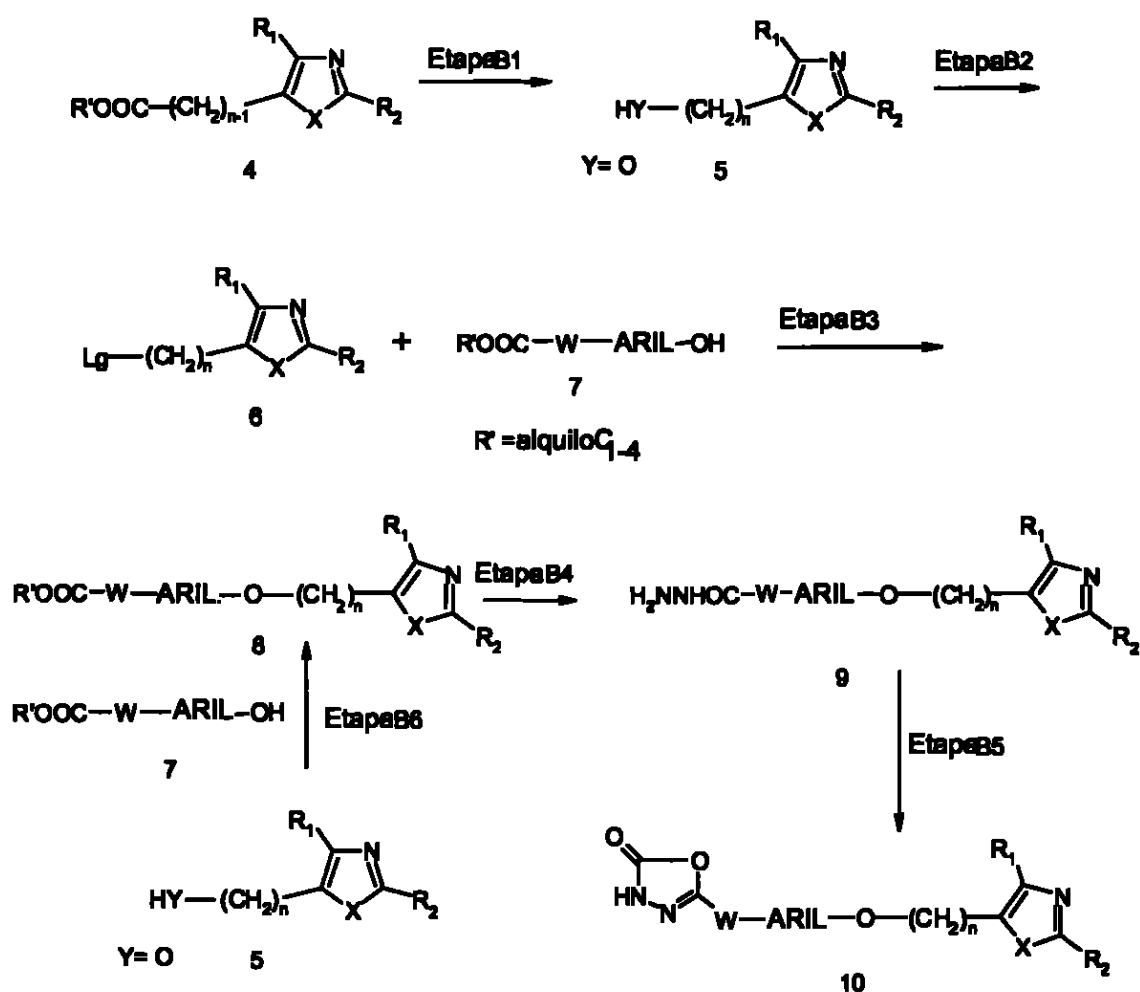
25 En la Etapa B3 se hace reaccionar un hidroxi aril éster, 7, con el heterociclo, 6, para desplazar al grupo saliente para proporcionar el éster acoplado, 8. La reacción de desplazamiento se lleva a cabo bajo condiciones bien conocidas en la técnica. Típicamente la reacción se lleva a cabo en presencia de una base tal como hidruro sódico u otras bases inorgánicas tales como carbonatos alcalinos o hidróxidos alcalinos en un disolvente inerte. La temperatura de la reacción, aunque no es crítica, es de $0^\circ C$ a la temperatura de reflujo del disolvente inerte.

A continuación el compuesto 8, en la Etapa B4 se trata con hidracina sola o en un disolvente orgánico adecuado a temperaturas elevadas para dar la hidracida de ácido, 9. Típicamente la reacción se lleva a cabo a una temperatura de entre 50°C y la temperatura de reflujo del disolvente orgánico.

- 5 La ciclación de la hidracida de ácido 9, en la Etapa B5, a las 1,3,4-oxadiazol-2-onas, 10, objetivo se lleva a cabo por tratamiento del compuesto 9 con un cloroformiato en presencia de una base orgánica tal como piridina seguido por tratamiento con una base fuerte de amina impedida tal como 1,8-diazabicyclo[5.4.0]undec-7-eno (DBU) en un disolvente orgánico adecuado tal como acetonitrilo en un tubo sellado a temperatura elevada. Típicamente, la reacción se puede llevar a cabo desde 100°C a 200°C. Las 1,3,4-oxadiazol-2-onas también se pueden sintetizar haciendo reaccionar el compuesto 9 con fosgeno. Véase Stempel, A., et al., *J. Org. Chem.* 1955, 20, 412.

- 15 En la Etapa B6, se ilustra una síntesis alternativa del éster acoplado, 8. Por consiguiente, el alcohol, 5, se puede hacer reaccionar con el hidroxiaril éster, 7, en presencia de una triaril o trialquilfosfina, tal como trifenilfosfina o tri-n-butilfosfina y azodicarboxilato de dietilo en un disolvente inerte, por ejemplo THF o diclorometano para proporcionar el éster acoplado 8. Típicamente la reacción se lleva a cabo a una temperatura entre temperatura ambiente y la temperatura de reflujo del disolvente inerte.

Esquema B



El Esquema C ilustra la síntesis del compuesto de fórmula I en el que Z es -
 5 $(CH_2)_n-Y-(CH_2)_n-$. El esquema es más útil para sintetizar compuestos en los que n representa 1 o 2 en la cadena de alquileo unida al ARILO. En la Etapa C1 el compuesto 5 ($Y=O$) se convierte en el compuesto 6 (en el que Lg es cloro o bromo) como se describe en el Esquema B, Etapa B2. A continuación el compuesto 6 se hace reaccionar con tiourea, compuesto 11, bajo condiciones similares a las encontradas en Treau, M. et al.
 10 *Heterocycles*, 2001, 55 (9), 1727-1735, para producir el tiol, 5a.

Quando el compuesto 6 se hace reaccionar con una amina primaria 12, se produce el aminoalquil heterociclo 5b. Este desplazamiento de un grupo saliente por una ami-

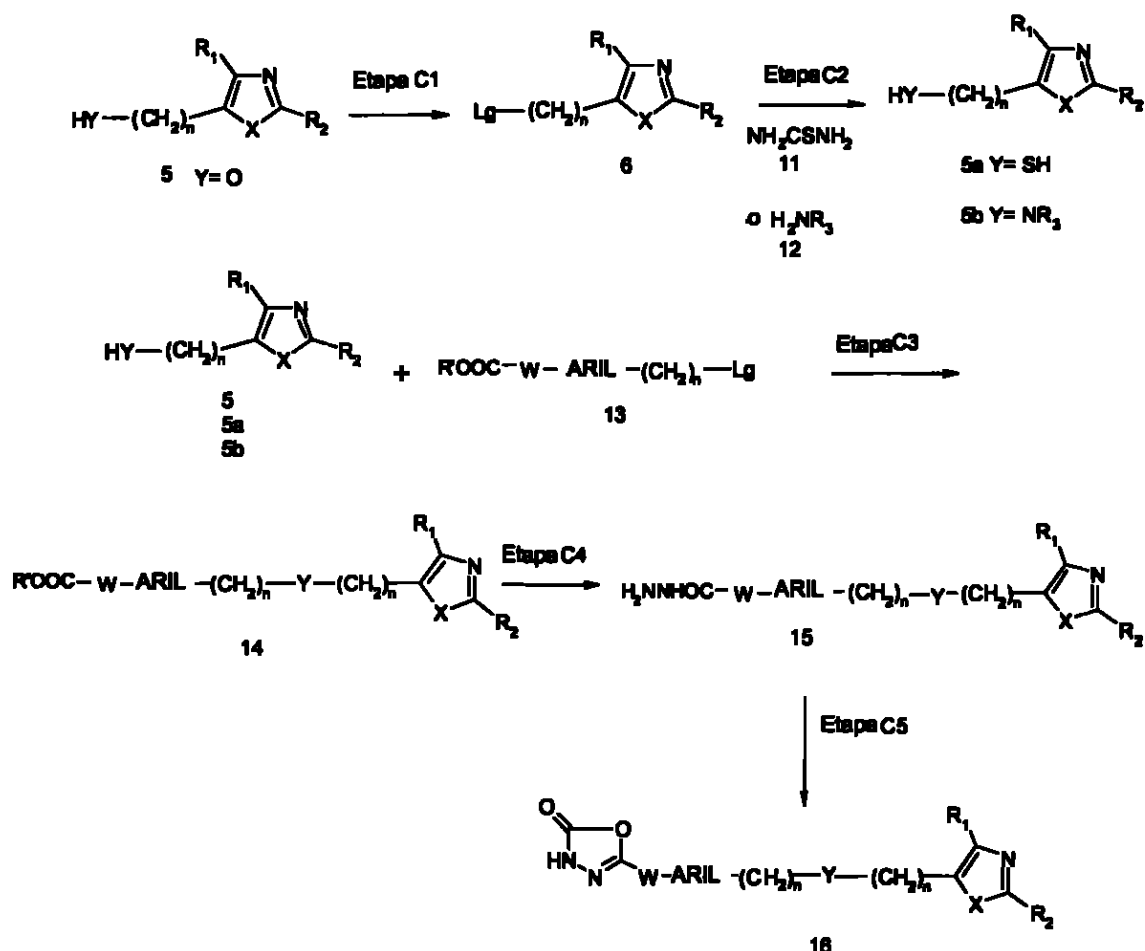
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na es bien conocido por los expertos en la técnica. Típicamente, la reacción de desplazamiento se lleva a cabo en un disolvente orgánico polar en presencia de una base orgánica que actúa como un captador de ácido. Aunque no es crítico, la reacción de desplazamiento se lleva a cabo a una temperatura de entre temperatura ambiente a temperatura de reflujo del disolvente.

En la Etapa C3 los compuestos 5, 5a y 5b se pueden hacer reaccionar con el compuesto 13 para proporcionar el ariléster, 14, en el que Y es O, S o NR₃. Así, cuando los compuestos 5 (Y = O) y 5a (Y = S) se hacen reaccionar con 13 para desplazar al grupo saliente, la reacción se llevará a cabo típicamente en presencia de una base fuerte, por ejemplo hidruro sódico, en un disolvente polar aprótico, tal como DMF o DMSO a temperaturas de aproximadamente entre 0°C a 150°C. Cuando el compuesto 5b (Y = NR₃) se hace reaccionar con 14, se utilizan condiciones idénticas a las descritas más arriba en la Etapa C2 para la amina primaria.

La síntesis de las 1,3,4-oxadiazol-2-onas 16 desecadas, a partir del compuesto 14 se lleva a cabo en dos etapas (C4 y C5) exactamente como se describe en el Esquema B, Etapas B4 y B5.

Esquema C



En el Esquema D se muestra una aproximación alternativa a los compuestos de fórmula I en los que Z es $-(CH_2)_n-Y-(CH_2)_n-$. El esquema es más útil para sintetizar compuestos en los que n es 3 a 5 en la cadena de alquileo unida al ARILO.

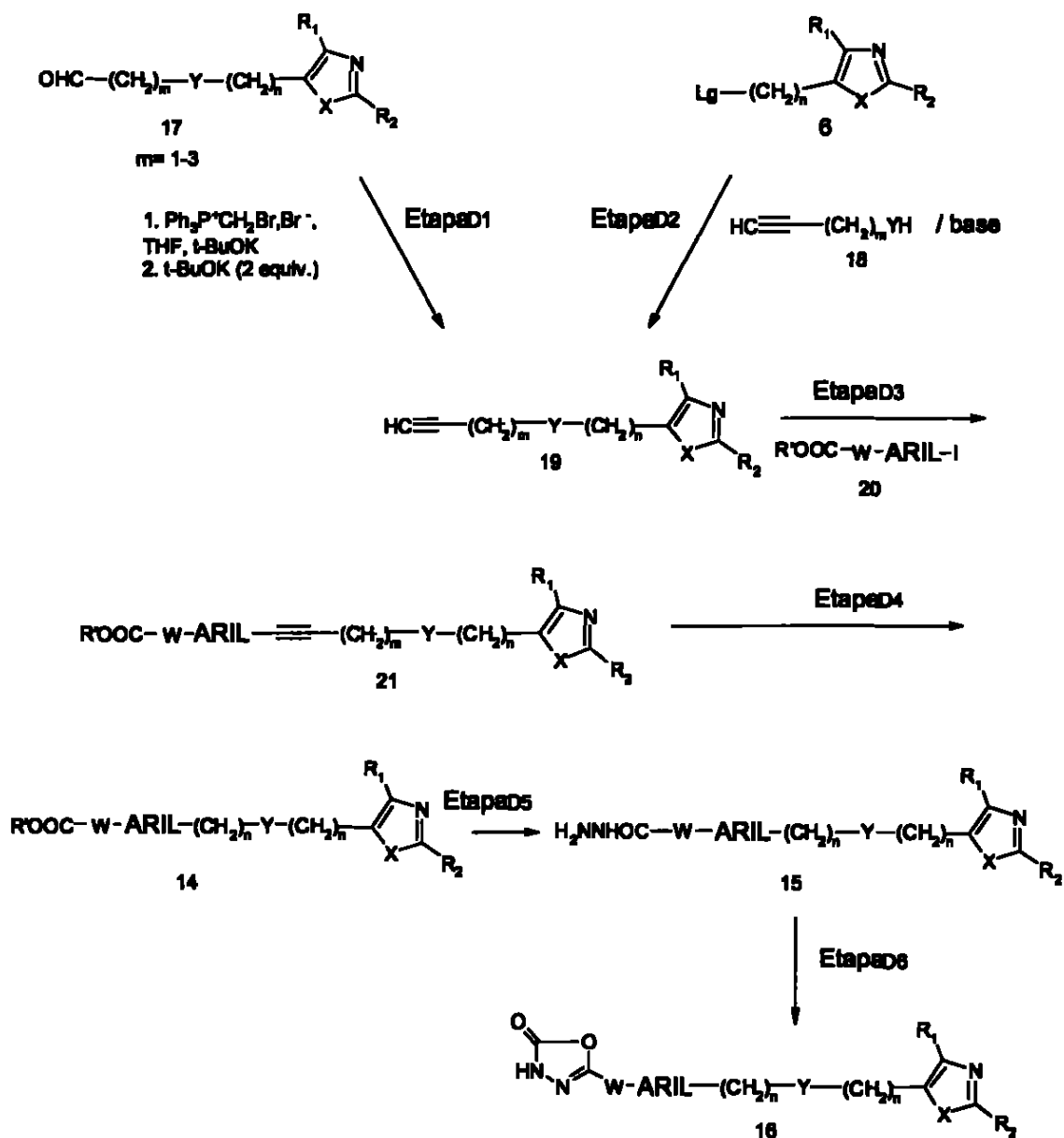
En la Etapa D1 el compuesto aldehído terminal 17, que se puede sintetizar por el método descrito en el Esquema A, se convierte en una secuencia de reacción en dos etapas en el acetileno terminal, 19. Así, la reacción de 17 con bromometilentrifenilfosforano (primera etapa) con terc-butóxido potásico t-BuOK produce una bromoolefina intermedia (no mostrada), que se trata posteriormente con 2 equivalentes de t-BuOK (segunda etapa) para formar el acetileno, 19. La secuencia de reacción para la conversión se describe en Pianetti, P., *Tet. Letters*, 1986, 48, 5853-5856. También, véase Corey, E. J., et al. *J. Am. Chem. Soc.*, 1969, 91, 4318-4320. Alternativamente, como se muestra en la

Etapas D2 los intermedios del tipo 19 se pueden preparar por desplazamiento de un grupo saliente a partir de un intermedio tal como 6 (véase el Esquema C) utilizando un nucleófilo, tal como 18, en el que esté incorporado un acetileno terminal.

5 En la Etapa D3, se efectúa el acoplamiento de Sonogashira del intermedio acetalénico, 19, con el yoduro de arilo, 20, en presencia de tetraquistrifenilfosfinapaladio (0), yoduro cuproso y una base orgánica adecuada en un disolvente inerte para rendir el acetileno terminal acoplado 21. A continuación se puede llevar a cabo la reducción del acetileno, 21, en la Etapa D4 por hidrogenación catalítica del compuesto 21 para dar el éster saturado 14. Típicamente, la reducción puede efectuarse por el uso de catalizadores
10 tales como paladio sobre carbón o clorotris(trifenilfosfina)rodio(I) en un disolvente orgánico inerte con hidrógeno a presiones entre 2 a 20 atm (30 a 300 p.s.i.). La reducción se puede llevar a cabo a una temperatura entre temperatura ambiente y 175°C.

La síntesis de las 1,3,4-oxadiazol-2-onas 16 deseadas, a partir del compuesto 14 se lleva a cabo en dos etapas (D5 y D6) exactamente como se describe en el Esquema B,
15 Etapas B4 y B5.

Esquema D



El esquema E ilustra una síntesis particular de compuestos de fórmula I en los que Z es $-(\text{CH}_2)_n\text{NR}_3(\text{CH}_2)_n-$. En esta aproximación, el enlazador Z se construye por una aminación reductora de un aldehído con una amina. Por ejemplo, en la Etapa E1 el tratamiento de 5b (en el que $\text{Y} = \text{NR}_3$) con un aldehído, tal como éster metílico del ácido 4-formil-benzoico ($n = 1$), compuesto 22, en un disolvente polar, normalmente un alcohol o una mezcla de alcohol THF, seguido por tratamiento con un agente reductor tal

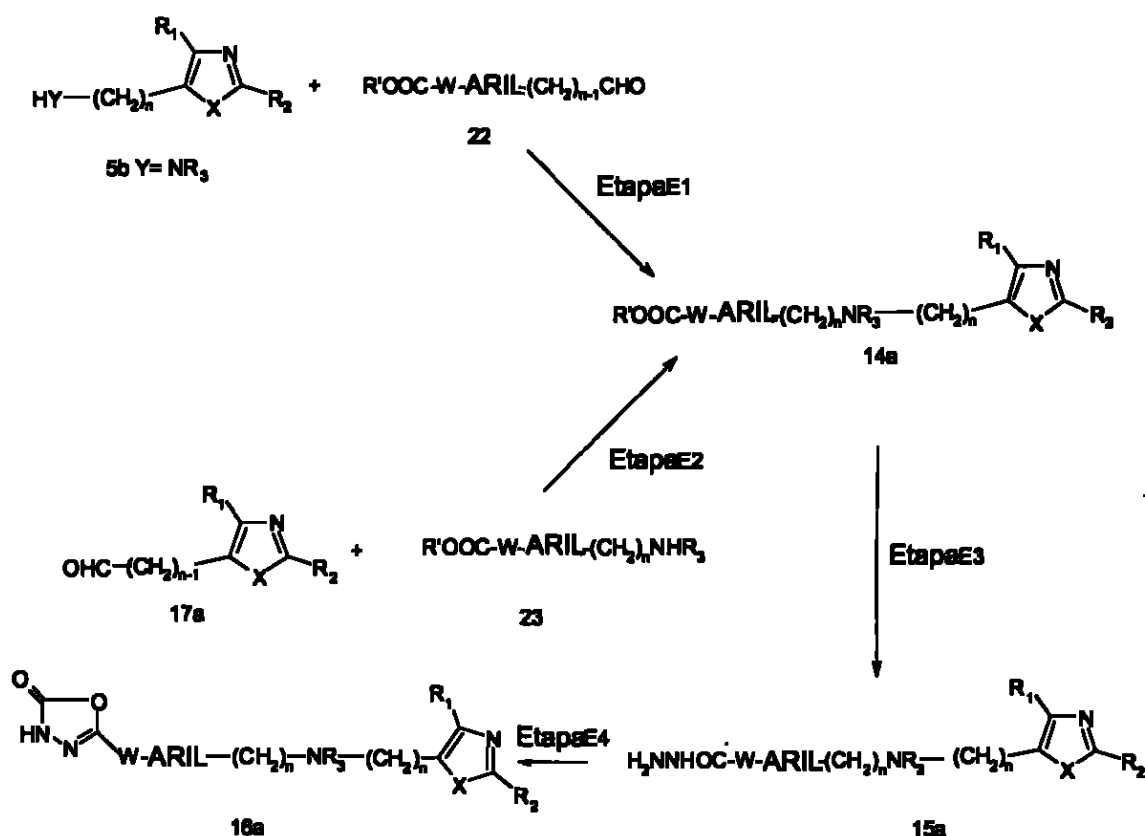
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como triacetoxi-borohidruro de sodio proporciona el intermedio 14a (n = 1) requerido.

Igualmente en la Etapa E2, el tratamiento de un aldehído tal como 17a con una amina, tal como el éster metílico del ácido 4-aminoalquil benzoico (n = 1), compuesto 23, proporciona 14a, en el que n es 1 y R₃ es H para -(CH₂)_nNR₃. El compuesto 14a en las etapas E3 y E4 se convierte en las 1,3,4-oxadiazol-2-onas 16a como se describe en el Esquema B, Etapas B4 y B5.

Más generalmente, se preparan aminas apropiadas (R'OOC-ARYL-(CH₂)_nNHR₃) a partir de los nitrilos o nitro compuestos correspondientes por hidrogenación catalítica o a partir de aminas acetilénicas y un yoduro o bromuro de arilo por acoplamiento de Sonogashira seguido por hidrogenación catalítica como se describe en el Esquema D.

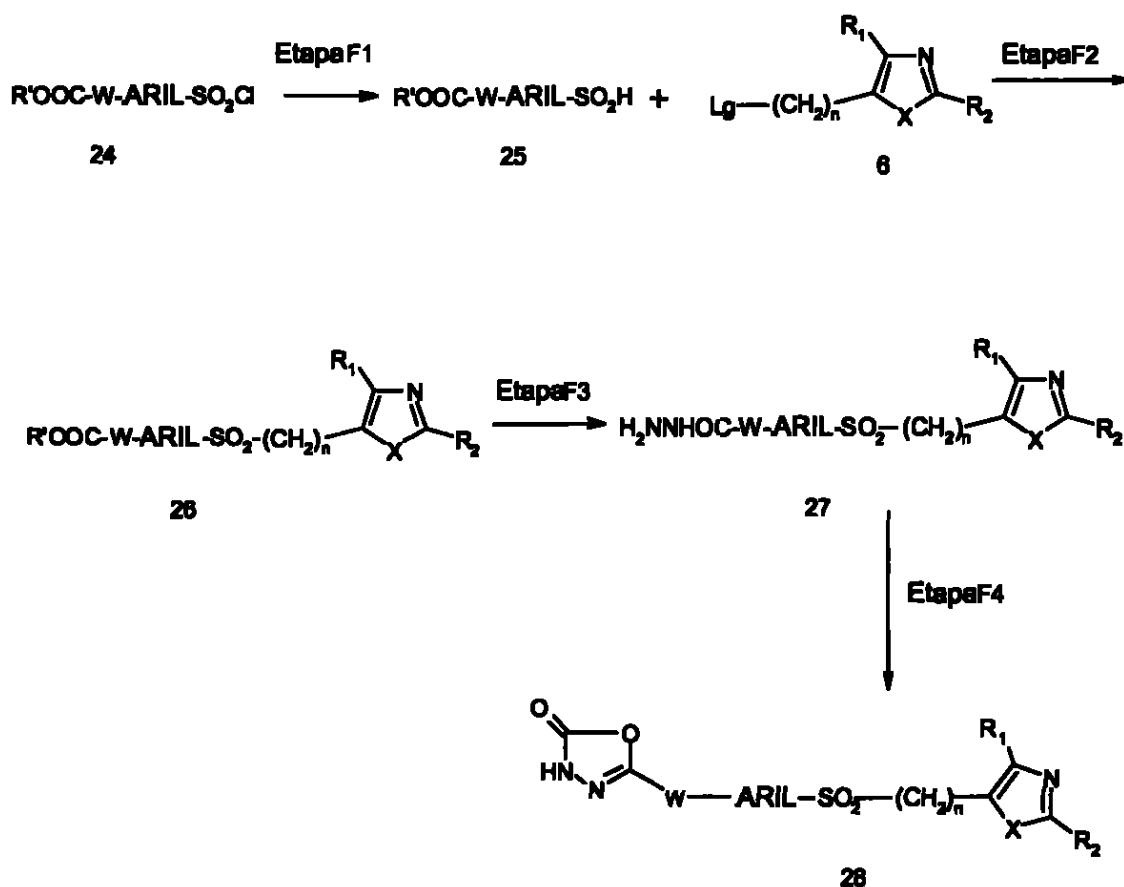
Esquema E



El Esquema F ilustra la síntesis de compuestos de fórmula I en los que Z es -SO₂ (CH₂)_n-. En la Etapa F1 el tratamiento de un cloruro de aril sulfonilo, 24, con sulfito sódico acuoso proporciona el ácido sulfinico, 25. La reacción de 25, como en la Etapa

F2, con un intermedio tal como 6 en un disolvente polar tal como DMF, acetonitrilo o etanol en presencia de una base tal como DBU, piridina, metóxido sódico o hidróxido sódico proporciona el intermedio 26. El intermedio 26 se convierte en la correspondiente 1,3,4-oxadiazol-2-ona, 28, en la Etapas F3 y F4 como se ilustra en el Esquema B, Etapas B4 y B5.

Esquema F

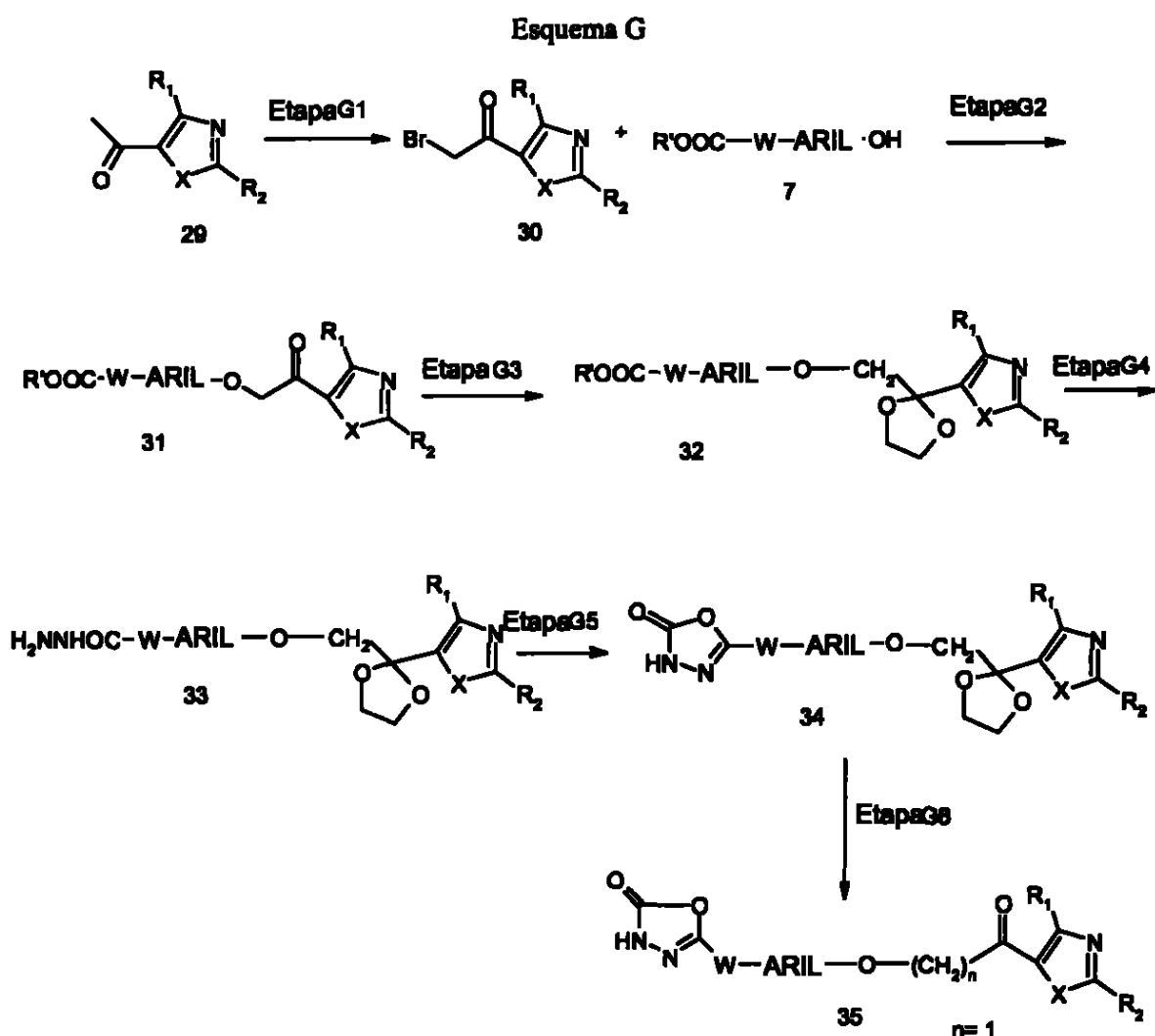


El Esquema G ilustra la síntesis del compuesto de fórmula I en el que Z es $-O(CH_2)_nCO-$. El esquema ilustra el caso en el que n es 1. El 2-acil heterociclo, 29, de partida se puede sintetizar a partir del correspondiente ácido carboxílico (preparado por el método ilustrado en el Esquema A) por adición de un reactivo de Grignard apropiado a una N-metoxi N-metil carboxamida intermedia Khlestkin, V.K. et al.; Current Organic Chemistry, 2003, 7(10), 967-993. y Singh, J. et al., Journal für Praktische Chemie, 2000, 342, 340-347). La preparación de la N-metoxi N-metil carboxamida intermedia se

lleva a cabo más convenientemente por reacción del ácido con hidrocloreuro de N-metoxi-N-metil hidroxilamina en presencia de un reactivo de acoplamiento de péptidos tal como EDC, DCC, DMPU y una base de amina terciaria tal como diisopropiletilamina o trietilamina.

- 5 Así bajo control, se broma 29 para producir la bromocetona 30, como se muestra en la Etapa G1. La bromación se puede llevar a cabo por métodos bien conocido, por ejemplo reacción de 29 con bromuro de piridinio por bromuro en ácido acético o reacción de 29 con Br₂ en un disolvente orgánico inerte tal como el diclorometano. Se hace reaccionar la bromocetona 30 resultante, en la Etapa G2, con el arilhidroxi éster 7 bajo
- 10 las condiciones descritas en el Esquema B (Etapa B3) para proporcionar el éster acoplado 31. La funcionalidad cetona en 31 se protege como un cetal 32, como se muestra en la Etapa G3 por métodos bien conocidos en la técnica. A continuación el compuesto 32 se convierte en el cetal de la 1,3,4-oxadiazol-2-ona 34, en las Etapas G4 y G5 por la secuencia estándar como se describe en el Esquema B (B4 y B5). Finalmente, en la Etapa
- 15 G6, la funcionalidad cetal en 34 se escinde, por ejemplo, con ácido mineral en THF-metanol-agua u otros métodos conocidos en la técnica para proporcionar la estructura objetivo 35.

- Sería evidente para los expertos en la técnica que el anterior procedimiento del Esquema G se podría utilizar para sintetizar análogos del compuesto 35 en los que n es
- 20 2-5 comenzando con una bromocetona, compuesto 30, con un sustituyente bromoalcanoilo más largo (Br(CH₂)_nCO-, en el que n es 2 a 5).

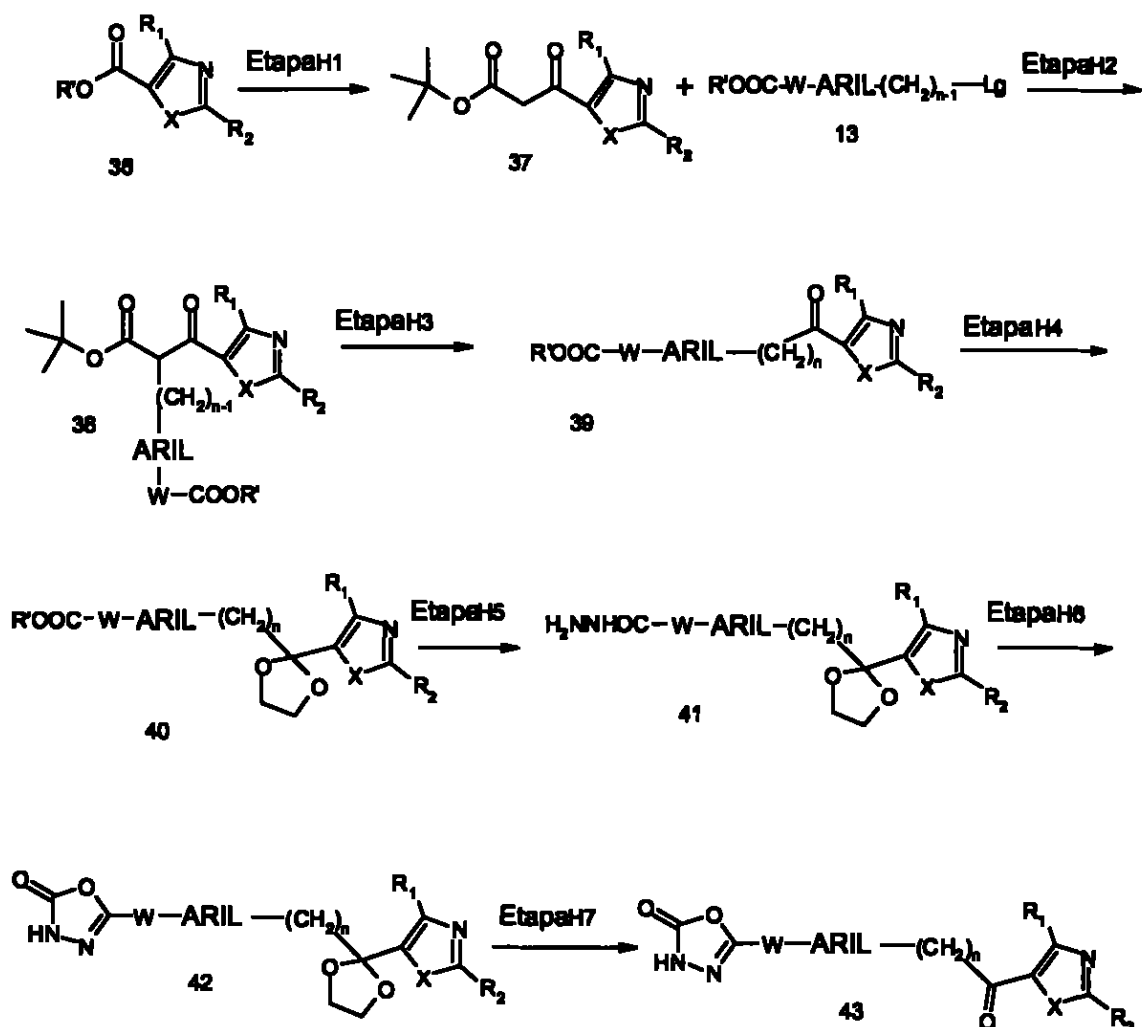


El Esquema H ilustra el procedimiento para la preparación de compuestos de fórmula I en los que Z es $-(CH_2)_nCO-$. En la Etapa H1, se trata el heterociclo sustituido con metoxycarbonilo apropiado, 36, con 2 equivalentes del enolato de litio del acetato de t-butilo en un disolvente tal como THF o DME a una temperatura que se extiende desde $-78^\circ C$ a temperatura ambiente para proporcionar el cetoacetato intermedio 37. En la Etapa H2, el tratamiento de 37 con una base tal como hidruro sódico en un disolvente inerte a temperatura entre $-10^\circ C$ y temperatura ambiente seguido por alquilación del anión resultante con un electrófilo tal como 13 rinde el cetodiéster intermedio avanzado 38. La descarboxilación se muestra en la Etapa H3 y puede llevarse a cabo primero por tratamiento de 38 con TFA en un disolvente inerte tal como diclorometano seguido por termólisis a una temperatura entre $70^\circ C$ y $150^\circ C$ para proporcionar el cetoéster interme-

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5 dio 39. La funcionalidad cetona en 39 se protege como un cetal 40, como se muestra en la Etapa H4 por métodos bien conocidos en la técnica. A continuación el compuesto 40 se convierte en el cetal de la 1,3,4-oxadiazol-2-ona 42, en las Etapas H5 y H6 por la secuencia estándar como se describe en el Esquema B (B4 y B5). Finalmente, en la Etapa H7, la funcionalidad cetal en 42 se escinde, como se describe anteriormente en el Esquema G, Etapa G6 para proporcionar la 1,3,4-oxadiazol-2-ona deseada, compuesto 43.

Esquema H



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Ejemplos biológicos:

Los siguientes protocolos de ensayo se usan para evaluar las propiedades biológicas de los compuestos de esta invención. Los siguientes ejemplos se presentan para

ilustrar adicionalmente la invención. Sin embargo, no deben considerarse limitantes de la invención de ninguna manera.

Determinación de los valores de EC₅₀ en el ensayo PPARdelta-GAL4 basado en células:

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Principio

Se analiza la potencia de sustancias, que se unen al PPAR delta humano y lo activan de una manera agonista, utilizando una línea celular HEK establemente transfectada (HEK siglas en inglés de riñón embrionario humano, HEK = human embryo kidney) que se refiere en la presente memoria como línea celular indicadora de PPAR delta. La línea celular indicadora de PPAR delta contiene dos elementos genéticos, un elemento indicador de luciferasas (pdeltaM-GAL4-Luc-Zeo) y una proteína de fusión de PPAR delta (GR-GAL4-PPAR delta humano-LBD), que media la expresión del elemento indicador de luciferasa dependiendo de un ligando del PPAR delta. La proteína de fusión estable y constitutivamente expresada GR-GAL4-PPAR delta humano-LBD se une en el núcleo celular de la línea celular indicadora de PPAR delta vía la porción de proteína GAL4 a los motivos de unión al ADN del GAL4 en dirección 5' del elemento indicador de luciferasa que está establemente integrado en el genoma de la línea celular. En ausencia de un ligando del PPAR delta hay solo poca expresión del gen indicador de luciferasa si en el ensayo se utiliza suero fetal bovino empobrecido en ácido graso (cs-FCS). Los ligandos del PPAR delta se unen y activan la proteína de fusión de PPAR delta y de ese modo estimulan la expresión del gen indicador de luciferasa. La luciferasa, que se forma se puede detectar por medio de quimioluminiscencia vía un sustrato apropiado.

25 Construcción de la línea celular indicadora de PPAR delta:

La producción de la línea celular indicadora de PPAR delta estable se basa en un clon estable de células HEK que fue establemente transfectado con un elemento indicador de luciferasa. Esta etapa ya se describió más arriba en la sección "construcción de la línea celular indicadora de PPAR alfa". En una segunda etapa, la proteína de fusión de PPAR delta (GR-GAL4-PPAR delta humano-LBD) fue establemente introducida en este clon celular. Para este propósito, el ADNc que codifica los 76 aminoácidos N-

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terminales del receptor de glucocorticoides (n° de acceso P04150) se unió a la sección de ADNc que codifica los aminoácidos 1-147 del factor de transcripción de levadura GAL4 (n° de acceso P04386). El ADNc del dominio de unión con el ligando del receptor PPAR delta humano (amino ácidos S139-Y441; n° de acceso # L07592) se clonó en el extremo 3' de esta construcción GR-GAL4. La construcción de fusión preparada de este modo (GR-GAL4-PPAR delta humano-LBD) se reclonó dentro del plásmido pcDNA3 (Invitrogen) para permitir la expresión constitutiva por el promotor del citomegalovirus. Este plásmido se linealizó con una endonucleasa de restricción y se transfectó establemente en el clon celular previamente descrito que contenía el elemento indicador de luciferasa. La línea celular indicadora de PPAR delta resultante que contiene un elemento indicador de luciferasa y constitutivamente expresa la proteína de fusión de PPAR delta (GR-GAL4-PPAR delta humano-LBD) se aisló por selección con zeocina (0,5 mg/ml) y G418 (0,5 mg/ml).

15 Procedimiento de ensayo y evaluación:

La actividad de los agonistas del PPAR delta se determina en un ensayo de 3 días, que se describe más abajo:

20 Día 1

La línea celular indicadora de PPAR delta se cultiva al 80% de confluencia en DMEM (# 41965-039, Invitrogen) que se mezcla con las adiciones siguientes: cs-FCS al 10% (suero fetal bovino; #SH-30068.03, Hyclone), 0,5 mg/ml de zeocina (#R250-01, Invitrogen), 0,5 mg/ml de G418 (#10131-027, Invitrogen), disolución de penicilina-estreptomicina al 1% (#15140-122, Invitrogen) y L-glutamina 2 mM (#25030-024, Invitrogen). El cultivo se lleva a cabo en botellas de cultivo celular patrón (# 353112, Becton Dickinson) en un incubador de cultivo celular a 37°C en presencia de CO₂ al 5%. Las células confluentes al 80% se lavan una vez con 15 ml de PBS (#14190-094, Invitrogen), se tratan con 3 ml de disolución de tripsina (#25300-054, Invitrogen) a 37°C durante 2 min, se recogen en 5 ml de la disolución de DMEM descrita y se cuentan en un contador celular. Después de dilución a 500.000 células/ml, se siembran 35.000 células en un volumen de 180 µL en cada pocillo de una placa de microvaloración de 96 po-

cillos con una base de plástico transparente (#3610, Corning Costar). Las placas se incuban en el incubador de cultivo celular a 37°C y con CO₂ al 5% durante 24 h.

Día 2

- 5 Los agonistas del PPAR delta que se van a probar se disuelven en DMSO en una concentración de 10 mM. Esta disolución de almacenamiento se diluye en DMEM (#41965-039, Invitrogen) que se mezcla con cs-FCS al 5% (#SH-30068.03, Hyclone), L-glutamina 2 mM (#25030-024, Invitrogen) y los antibióticos previamente descritos (zeocina, G418, penicilina y estreptomycin).
- 10 Las sustancias de ensayo se ensayan con 11 concentraciones diferentes en el intervalo de 10 µM a 100 pM. Los compuestos más potentes se ensayan con concentraciones en el intervalo de 1 µM a 10 pM o entre 100 nM y 1 pM.

- El medio de cultivo de la línea celular indicadora de PPAR delta sembrada en el día 1 se retira completamente o no se retira, y las sustancias de ensayo diluidas en medio se añaden inmediatamente a las células. La dilución y adición de las sustancias se lleva a cabo mediante un robot (Beckman FX). El volumen final de las sustancias de ensayo diluidas en medio es 100 µl por pocillo de una placa de microvaloración de 96 pocillos. La concentración de DMSO en el ensayo es menor de 0,1 % en vol/vol con el fin de evitar efectos citotóxicos del disolvente.
- 15

- 20 Cada placa se cargó con un agonista patrón del PPAR delta, que se diluyó igualmente en 11 concentraciones diferentes, para demostrar el funcionamiento del ensayo en cada placa individual. Las placas de ensayo se incuban en un incubador a 37°C y CO₂ al 5% durante 24 h.

- Alternativamente, se añaden directamente 20µL de una 10x concentración final de la sustancia de ensayo a los 180 µL que contienen las células sembradas. Las sustancias de ensayo se probaron en 8 concentraciones diferentes, por triplicado, en esta disposición de placa de ensayo.
- 25

Día 3

- 30 Las células indicadoras de PPAR delta tratadas con las sustancias de ensayo se retiran del incubador, y el medio se aspira. Las células se lisan pipeteando 50 µl de reactivo Bright Glo (de Promega) en cada pocillo de una placa de microvaloración de 96

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pocillos. Después de incubar a temperatura ambiente en la oscuridad durante 10 minutos, las placas de microvaloración se miden en el luminómetro (Trilux de Wallac). El tiempo de medición para cada pocillo de la placa de microvaloración es 1 segundo.

5 **Evaluación:**

Los datos sin procesar del luminómetro se transfieren a un fichero de Microsoft Excel. Los gráficos dosis-efecto y los valores de EC_{50} de los agonistas del PPAR se calculan utilizando el programa XL.Fit como se especifica por el fabricante (IDBS).

10 Se midieron los valores de EC_{50} del PPARdelta en el intervalo de 1nM a >10 μ M para los moduladores del PPAR de los ejemplos en esta solicitud. Los compuestos de la invención de fórmula I pueden actuar como agonistas o antagonistas. Más abajo se describe el ensayo para determinar la actividad agonista parcial o antagonista.

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Determinación de la Eficacia de Agonistas Parciales o Antagonistas en el Receptor PPARdelta

20 Este ensayo determina si los compuestos actúan como agonistas parciales o antagonistas en el receptor PPARdelta.

La siembra y cosecha de las placas de ensayo son como se describen en el Día 1 y 3 más arriba.

Día 2

25 El agonista parcial o el antagonista y un agonista selectivo conocido se diluyen en DMEM (#41965-039, Invitrogen), que se mezcla con cs-FCS al 10% (#SH-30068.03, Hyclone), L-glutamina 2 mM (#25030-024, Invitrogen) y los antibióticos previamente descritos (zeocina, G418, penicilina y estreptomycin) a 20X concentraciones finales deseadas. Se añaden diez microlitros del agonista parcial o el antagonista a la placa de ensayo que contiene las células. Las placas de ensayo se incuban en un incubador a 37°C y CO₂ al 5% durante 30 minutos. A continuación se añaden diez microlitros de los 20X agonistas selectivos conocidos, después de la pre-incubación del agonista parcial o el antagonista. Las placas de ensayo se incuban en un incubador a 37°C y CO₂

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al 5% durante 24 h. Para cada concentración de agonista parcial o antagonista se determina el efecto sobre las EC_{50} de los agonistas selectivos conocidos.

Ensayo de Unión SPA PPAR delta-LBD

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Disoluciones de Almacenamiento:

Tris 1 M (pH = 8,0 o pH = 7,6) (Gene Medicine Stock Room)

KCl 2 M (Polvo en N2140)

10

Tween 20

DTT 100 mM

GW2331 13,9 μ M en EtOH CALIENTE

GW 2331 10 mM en DMSO FRIO

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PPAR-alpha (varias Conc.)

Ej: ,884 μ g/ μ l

Tampón de Lavado:(Almacenar a 4⁰C. El tampón es válido durante una semana)

20

Tris 10 mM (pH = 7,6 u 8) 10 ml

KCl 50 mM 25 ml

Tween 20 al 0,05 % 0,5 ml

Agua de Millipore 964,5

25

Comprobar que PH = 7,6

Tampón de Unión:(Preparar tampón de unión reciente cada vez)

Tampón de Lavado 50 ml

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DTT 10 mM 5,5ml

Preparación de los Reactivos de Reacción para 1 Placa:

Perlas de SPA Recubiertas de Glutación

- 5 Cada botella de perlas de SPA contiene 500 mg de perlas
Reconstituir 500mg de perlas de SPA en 5 ml de tampón de lavado, y será válido durante dos o tres semanas
Almacenar a 4°C
- 10 **Preparar perlas de SPA diluidas en el tampón de unión.**

Añadir 1 ml de las perlas de SPA reconstituidas de más arriba a 60 ml de tampón de Unión
añadir 20 µl de las perlas diluidas de más arriba a cada pocillo de una placa de 96 pocillos.
15 llos.

Utilizar 2 ml de las perlas diluidas de más arriba para cada placa (sin incluir volumen muerto).
- 20 3H GW-2331 más GST-PPAR delta-LBD (para una placa de 96 pocillos sin volumen muerto) 13,9 µM 40nM / pocillo

3,0 ml/placa (Incluyendo el volumen muerto)
Si la actividad específica de 3H-GW2331 es 1 mci/ml (de Amersham), diluir 17 µl de
25 3H GW-2331 en 3,0 ml de Tampón de Unión = ,08 µM

Si la concentración de proteína es 1 mg/mL, añadir 21 µl de proteínas en 3,0 ml de tampón de unión.
- 30 En Resumen: UNA placa de 96 pocillos: 3000 µL de Tampón de Unión + 17 µL de 3H-GW2331 + 21 µL de GST-PPAR-delta (1 mg/ml)

Placas de Control

Una Placa Madre de 96 pocillos (Para 2 Placas de control)

5 En la columna #1:

Añadir 5 µl de GW2331(10 mM) frío a los pocillos E-H.

Añadir 45 µL de DMSO a los pocillos A-H.

En la columna #12 (dilución triple):

10 Añadir 10 µl de GW2331 (10 mM) frío al pocillo A.

luego añadir 90 µl de DMSO al pocillo A, mezclar bien la disolución.

añadir 20 µl de DMSO a los pocillos B-H.

llevar 10 µl de disolución desde el pocillo A al B, mezclar bien,

después llevar 10 µl de disolución desde B a C, mezclar bien,

15 luego llevar 10 µl de disolución desde C a D, mezclar bien.

.....

Finalmente, llevar 10 µl desde F a H.

Una Placa de control (para 8 Placas de Reacción)

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Una placa de control es la dilución 1:10 de la placa madre. El tampón de dilución es el tampón de lavado.

Placas de muestras

25

A una placa biblioteca de CPC reciente, añadir 90 µl de DMSO

Tomar 10 µl de disolución de DMSO y añadirlos a 90 µl de tampón de lavado en una placa de muestras

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Placas de Reacción:

Añadir 20 µl de perlas de SPA y 30 µl de 3H-GW2331 con GST-PPAR-delta a cada pocillo de una Placa de Reacción.

- 5 Añadir 5 µl de los compuestos desde cada pocillo de la placa de muestras en las columnas 2 a 11 de una placa de reacción.

Añadir 5 µl de los compuestos desde la columna 1 y la columna 12 de la placa de control a la columna 1 y la columna 12 de la placa de reacción.

- 10 **Protocolo de SPA de 96 pocillos:**

Dejar equilibrar las placas de reacción durante 20 minutos a 2 horas.

Sellar las placas antes de contar en un contador Microbeta (Wallac).

- 15

Calcular las IC₅₀.

En el Ensayo de Unión PPAR delta-LBD de SPA se midieron valores de IC₅₀ en el intervalo de 1 nM a >10 µM para los moduladores del PPAR de los ejemplos en esta solicitud. Los compuestos de la invención de fórmula I pueden actuar como agonistas o antagonistas.

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Cultivos de Oligodendrocitos de RATA/RATÓN

- 25 **Preparación de células:**

1. Las células primarias progenitoras de oligodendrocitos de rata se obtienen a partir de la neocorteza de ratas o ratones recién nacidos (días posnatales 2-3) y se enriquecen, después de la eliminación de la microglia, mediante separación mecánica a partir de la monocapa astrocítica utilizando una modificación de la técnica originalmente descrita por McCarty y de Vellis (1980).

- 30

2. Quitar las meninges del cerebro de rata neonatal y disociar mecánicamente el tejido. Sembrar las células en matraces T75 y alimentar las células con

DMEM/F12 + FBS al 10%.

3. Recoger los oligodendrocitos que crecen sobre la capa lecho de astrocitos por el método de agitación catorce días después de la fecha de preparación original. Centrifugar la suspensión y resuspender el sedimento celular en medios libres de suero (SFM; DMEM combinado con 25 µg/ml transferrina, triyodotironina 30 nM, hidrocortisona 20 nM, progesterona 20 nM, biotina 10 nM, 1x oligoelementos, selenio 30 nM, 1 µg/ml de putrescina, BSA al 0,1%, 5 U/ml de PenStrep, 10 µg/ml de insulina) suplementados con los factores de crecimiento siguientes: Factor de crecimiento derivado de la plaqueta-AA (PDGF) y factor de crecimiento de los fibroblastos 2 (FGF).
4. Sembrar las células sobre placas recubiertas con PDL e incubar a 37°C con CO₂ al 6-7%.
5. Los componentes de los medios de cultivo se reponen cada 48 horas para mantener a las células en un estado progenitor.

Realización de pases por el medio de cultivo de las células progenitor para aumentar el número de células para los ensayos de detección sistemática:

1. Cuando el cultivo es confluyente, enjuagar el cultivo con PBS, añadir tripsina e incubar durante ~2-3 min a 37°C.
2. Neutralizar y centrifugar la suspensión celular a 900 g durante 5 min.
3. Resuspender el sedimento celular en SFM + PDGF/FGF.
4. Alimentar las células con factores de crecimiento recientemente preparados cada 48 horas para mantenerlas enriquecidas para dividir rápidamente las células progenitor.
5. Las células no se pasan más de 4-5 veces antes de los ensayos experimentales.
6. Todos los experimentos que implicaban células progenitoras de oligodendrocitos se hicieron utilizando células que se mantuvieron continuamente bajo estas condiciones. Más del 95% de todas las células fueron inmunopositivos A2B5 y expresaron ARNm 2' 3' -nucleótido cíclico 3' -fosfodiesterasa II.
7. Para general oligodendrocitos maduros, 24 h después de sembrar las células progenitor se cambiaron a SFM suplementado con o sin IGF-I y se cultivaron bajo estas condiciones durante 7 d antes de los ensayos experimentales.

8. Alternativamente, se puede utilizar la línea celular progenitora de Glía Central 4 (CG4) de rata enriquecida, que se mantiene en medios base (DMEM, con glutamina 2 mM, piruvato sódico 1 mM, biotina (40 nM), insulina (1 μ M) y N1) suplementados con 30% de medio acondicionado a partir de la línea celular de neuroblastoma B-104. Para inducir diferenciación, las células CG4 se cambian a medios base con suero fetal bovino al 1% (eliminado después de 2 días) e insulina (500 nM). Se utiliza la inmunorreactividad A2B5 y MBP para confirmar un enriquecimiento >95% en cultivos inmaduros y maduros, respectivamente.
- 5
- 10 Tratamiento con Compuesto del Cultivo Rata/Ratón:
1. Poner 10.000 – 15.000 células/pocillo en placas recubiertas de PDL de 24 pocillos y cultivar las células en presencia de mitógeno (10 ng/ml) durante toda la noche.
 2. En presencia de mitógeno:
 - 15 a. Día siguiente, eliminar el medio viejo y añadir los compuestos en medio (con mitógeno) recientemente preparado
 - b. Las evaluaciones de la dosis respuesta de los compuestos se llevan a cabo a 6 concentraciones diferentes (10 μ M, 1 μ M, 100 nM, 10 nM, 1 nM, y 0,1 nM);
 - 20 c. Se desarrollan pocillos triplicados para cada concentración de compuesto.
 3. En ausencia de mitógeno:
 - a. Día siguiente, eliminar el medio viejo y añadir los compuestos en medio (sin mitógeno) recientemente preparado
 - 25 b. Las evaluaciones de la dosis respuesta de los compuestos se llevan a cabo en 6 concentraciones (10 μ M, 1 μ M, 100 nM, 10 nM, 1 nM, y 0,1 nM);
 - c. Se desarrollan pocillos triplicados para cada concentración de compuesto.
 - 30 4. Cultivar las células tratadas durante 7 d antes de utilizarlas en los ensayos experimentales.

Cultivos de Oligodendrocitos HUMANOS

Preparación de células:

1. Se cultivan neuroesferas humanas recogidas a partir de corteza de embrión humano E19,5 - E22 durante 2 semanas en medio progenitor (DMEM/F12 que contiene 100 µg/ml de transferrina, triyodotironina 30 nM, hidrocortisona 20 nM, progesterona 20 nM, biotina 10 nM, 1x oligoelementos, selenio 30 nM, putrescina 60 µM, BSA al 0,1%, 5 U/ml de PenStrep, 25 µg/ml de insulina) suplementado con PDGF y FGF.
2. Las neuroesferas se disocian con 20 U/ml de papaína a 37°C durante 30-50 min.
3. Las células se siembran en placas recubiertas de PDL a densidades de 50.000-100.000 células/pocillo en medio progenitor que contiene PDGF/FGF y se incuban a 37°C con CO₂ al 5-6%.
4. Los medios de cultivo y factores de crecimiento se reponen cada 48 horas.

Tratamiento con Compuesto del Cultivo Humano:

1. 24 a 48 horas después de sembrar, eliminar el medio viejo y añadir los compuestos en medio (con mitógeno) recientemente preparado
2. Las evaluaciones de la dosis respuesta de los compuestos se llevan a cabo a 3-6 concentraciones diferentes (10 µM, 1 µM, 100 nM, 10 nM, 1 nM, y 0,1 nM)
3. Se desarrollan pocillos triplicados para cada concentración de compuesto.
5. Cultivar las células tratadas durante 7 d antes de utilizarlas en los ensayos experimentales.

Inmunotinción Específica de oligodendrocitos de RATA/RATÓN/HUMANOS:

- Después de la exposición al compuesto, se utilizan los anticuerpos específicos de oligodendrocitos para valorar la capacidad del compuesto para acelerar/promover la diferenciación del oligodendrocito (por ejemplo, la inmunorreactividad a O4, O1, o a la proteína básica de mielina está prorrogada entre los cultivos tratados y no tratados con el compuesto).
1. Las células se siembran en portaobjetos con cámara de 4 pocillos tratados con poli-D-lisina en 5×10^3 a 20×10^3 células/pocillo y se cultivan como se describe más arriba. Se lleva a cabo la tinción secuencial sobre las poblaciones de oligo-

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dendrocitos con grados crecientes de diferenciación celular, como se determina por los días *in vitro* sin PDGF y FGF.

2. Se utiliza la tinción en vivo durante 30 min a 37°C para detectar la expresión del marcador específico de la superficie celular de la fase del oligodendrocito (incluyendo A2B5, O4, y O1).
3. Posteriormente, las células se fijan con paraformaldehído al 4%, 10 min, temperatura ambiente.
4. Se utilizan procedimientos de fijado de tinción para detectar la expresión del marcador específico de la fase del oligodendrocito (incluyendo la proteína básica de mielina, MBP).
5. Enjuagar con PBS.
6. Permeabilizar con Triton al 0,1% /NaAz al 0,01% diluido en 1X PBS durante 10 min, temperatura ambiente.
7. Bloquear con suero de cabra al 5-10% en tampón de dilución de anticuerpos (Triton-X 100 al 0,1% y 1% IgG-libre albúmina de suero bovino al 1%; también utilizado para diluir anticuerpos), 15 min, temperatura ambiente.
8. Añadir anticuerpo primario diluido en tampón de dilución de anticuerpos.
9. Incubar durante toda la noche, balanceando suavemente, a 4°C.
10. Al día siguiente, enjuagar con PBS 1X 5 min, seguido por 3X 15 min cada uno, temperatura ambiente.
11. Incubar con el anticuerpo secundario adecuado, 45 min, temperatura ambiente.
12. Se tiñe el núcleo celular con 4,6-diamidino-2-fenilindol (DAPI), 15 min, temperatura ambiente.
13. Enjuagar varias veces con PBS y evaluar utilizando microscopía de fluorescencia.
14. Se comparan las siguientes condiciones durante un periodo de tiempo y a diferentes dosis del compuesto: PDGF/FGF solo, SFM solo, SFM-IGF1 solo, PDGF/FGF y compuesto, SFM y compuesto.

Immunotinción con Bromodesoxiuridina (BrdU) de RATA/RATÓN/HUMANO:

- Para confirmar que los compuestos no promueven diferenciación celular.
1. Las células progenitoras de oligodendrocitos se marcan con 10 μ M de BrdU durante 20 horas y después se fijan o con etanol al 70% o con paraformalde-

- hído al 4%.
2. Las células se incuban sucesivamente con anti-BrdE de ratón biotinilada y Estreptavidina-Peroxidasa, con tres lavados intermedios con PBS.
 3. La visualización colorimétrica de la inmunorreactividad a BrdU se desarrolla con DAB y el número total de células se valora utilizando la contratinción con hematoxilina.
 4. Las células inmunopositivas a BrdU se cuentan por dos observadores independientes.
- 10 **Análisis de Imagen del Cultivo de RATA/RATÓN/HUMANO:** Se utiliza la microscopía de fluorescencia para cuantificar la extensión de la diferenciación de oligodendrocitos después de la exposición al compuesto. Este ensayo demuestra que los agonistas selectivos aceleran/promueven la diferenciación de los oligodendrocitos.
1. Recuento Manual de Células: Se seleccionan aleatoriamente cuatro campos para cada condición experimental y se cuentan 500-600 células en cada campo. Se compara el porcentaje de células inmunopositivas a MBP (u O4) (proceso maduro que lleva células con o sin capas de mielina) versus células positivas a DAPI (número total de células) en los grupos de control y tratados con fármaco.
 2. Recuento Automático de Células: Se utilizó la microscopía de fluorescencia para cuantificar la extensión de la diferenciación de oligodendrocitos después de la exposición al compuesto. Se seleccionaron aleatoriamente seis campos/pocillos para valorar el número de oligodendrocitos diferenciados de entre la población total (se cuentan ~8 a 15×10^3 células/pocillo). Se obtuvieron imágenes de inmunofluorescencia utilizando un sistema de imagen digital Zeiss AxioVision, con una cámara de CCD enfriado Zeiss AxioCam HRc conectada al mismo microscopio. Se establecieron todos los parámetros de imagen del microscopio para adquirir imágenes para el análisis de intensidad de inmunofluorescencia celular. Se comparó el porcentaje de células positivas a MBP (diferenciadas) versus las células totales (teñidas en el núcleo con DAPI) en los grupos control versus tratados con fármaco. La autofluorescencia celular fue indetectable bajo las condiciones de imagen.
 3. Ensayo de diferenciación de oligodendrocitos Humanos: Contar manualmente el

número total de células inmunopositivas a O4/pocillo (bipolar y multipolar).

En la Tabla 2 se muestran los resultados utilizando cultivos de oligodendrocitos de rata. Como muestran los resultados los compuestos de la presente invención potencian o aceleran la diferenciación de los oligodendrocitos de rata, según se mide por el aumento de la expresión de proteína básica de mielina comparada con los controles no tratados. Este hallazgo sugiere que los ejemplos de compuestos mostrados en la Tabla 2 potenciarían, acelerarían, o estimularían la diferenciación de los oligodendrocitos y la formación de mielina *in vivo*, en el SNC enfermo o lesionado, incluyendo MS y otros trastornos desmielinizantes.

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Tabla 2

Resultados para el Ensayo de Diferenciación de Oligodendrocitos Primarios de Rata

Ejemplo nº	Número de Veces de Aumento de la Expresión de la Proteína Básica de Mielina en el Ensayo de Diferenciación de Oligodendrocitos (concentración µM)
10	1,5 veces (10)
14	1,5 veces (1)
23	2 veces (1)
31	2 veces (1)

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Reacción en Cadena de la Polimerasa (PCR) Cuantitativa de RAT/RATÓN/HUMANO:

Para evaluar la activación de la ruta del PPAR delta inducida por el compuesto y la extensión de la maduración de los oligodendrocitos (cambios en los niveles del ARNm).

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1. Se extrae el ARN total de los oligodendrocitos cultivados utilizando el reactivo TriZol.
2. Posteriormente, se trata el ARNm con DNasa libre de RNasa, se repurifica, y a continuación se convierte en la plantilla de ADNc utilizando una reacción de RT (Clontech Advantage RT para el Kit de PCR).
3. La expresión de la transcripción del miembro de la ruta del PPAR delta se

cuantifica utilizando la mezcla maestra Sybr Green PCR Master Mix.

4. Se utiliza la mezcla de cebador/sonda de ARN ribosomal 18S (producto de 186 bp), suspendida en Taqman 2X PCR Master Mix como un control interno.
5. La PCR cuantitativa se lleva a cabo utilizando la tecnología en tiempo real de Taqman™ (Gibson, et al., 1996) con un sistema detector de secuencias Sequence Detector System modelo 7700 (Applied Biosystems, Foster City, CA).
6. Los resultados se analizan utilizando la versión 1.91 del programa informático Sequence Detection Systems.

Ensayo ELISA en RATA: Para evaluar la activación de la ruta del PPAR delta inducida por el compuesto y la extensión de la maduración de los oligodendrocitos (cambios en los niveles de proteína).

1. Las placas se lavan con PBS, y después se mantienen en hielo. Añadir 200 µl de tampón de lisis antiguo helado (Tris 50mM, pH 7,4, MgCl₂ 2mM, EDTA 1mM, β-mercaptoetanol 5mM, Nonidet P-40 al 1%, cóctel inhibidor de Proteasa (Roche): 1 comprimido/50 ml) a cada pocillo.
2. Lisar las células utilizando la pipeta arriba y abajo y centrifugar las placas a 2000 rpm a 4°C durante 5 min. El sobrenadante está listo para usarse.
3. Pipetear 50 µl de patrón, controles y muestras a los pocillos.
4. Añadir 50 µl de Tampón de Ensayo de MBP a cada pocillo.
5. Incubar el pocillo, agitando a 500-700 rpm en un agitador orbital de microplacas durante 2 horas a temperatura ambiente.
6. Añadir 100 µl del conjugado Anticuerpo de MBP-Biotina a cada pocillo.
7. Incubar el pocillo, agitando a 500-700 rpm en un agitador orbital de microplacas durante 1 hora a temperatura ambiente.
8. Lavar el pocillo 5 veces con Disolución de Lavado. Secar por transferencia invirtiendo la placa sobre material absorbente.
9. Diluir el conjugado estreptavidina-enzima concentrado 1:50 con tampón de Ensayo de Elisa de MBP. (debe diluirse inmediatamente antes de su uso en el ensayo).

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10. Añadir 100 µl de disoluciones de conjugado de estreptavidina-enzima a cada pocillo.
 11. Incubar el pocillo, agitando a 500-700 rpm en un agitador orbital de microplacas durante 30 minutos a temperatura ambiente.
 - 5 12. Lavar el pocillo 5 veces con la Disolución de Lavado. Secar por transferencia invirtiendo la placa sobre material absorbente.
 13. Añadir 100 µl de solución cromógena de TMB (TMB Chromogen Solution) a cada pocillo.
 14. Incubar el pocillo, agitando a 500-700 rpm en un agitador orbital de microplacas durante 10-20 minutos a temperatura ambiente. Evitar la exposición a la luz solar directa.
 - 10 15. Añadir 100 µl de la Disolución de Parada a cada pocillo.
- Leer la absorbancia de la disolución en los pocillos dentro de 30 minutos, utilizando un lector de microplacas ajustado a 450 nm.

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Modelos de Prueba de Concepto *In Vivo*

Lesiones Focales: (utilizadas para valorar si los compuestos protegen la integridad de la mielina o aceleran/potencian la velocidad de remielinización).

1. Se da libre acceso a la comida y el agua a ratas de 7 semanas de edad y se aclimatan durante un mínimo de 4 días antes de su uso en los experimentos.
- 20 2. Se pesa a cada animal antes de la cirugía. A continuación la rata se anestesia con ketamina (100 mg/ml) en combinación con xilazina (20 mg/ml) en una relación de 1,8 : 1. Se inyecta a las ratas con 0,15 ml/180 g de peso corporal i.p. de solución anestésica antes del procedimiento quirúrgico. Se prepara al animal para cirugía utilizando condiciones asépticas de acuerdo con las directrices del IACUC.
- 25 Se autoclavarán todos los instrumentos quirúrgicos. Se corta el pelo entre las orejas y esta región se limpiará frotando con Betadine, se limpiará chorreando con solución salina estéril y finalmente se secará con un algodón pre-empaquetado con alcohol estéril.
- 30 3. Para el procedimiento quirúrgico, la rata se coloca sobre su superficie ventral en un instrumento estereotáxico para pequeños animales diseñado para mantener la cabeza estable. La guía incisiva se ajusta siempre a -3,9 mm, ya que se ha de-

mostrado que esto logra una posición de cráneo plano para ratas SD.

4. Se hace una incisión en la piel previamente afeitada suprayacente al cráneo entre las orejas.
5. Se perfora una pequeña zona del hueso (0,75 mm de diámetro) en las coordenadas siguientes AP -1,8, ML -3,1 desde lambda.
6. Se quita el hueso y se inyecta a las ratas con 2µl de bromuro de etidio, lisolecitina, o SIN-1 en el pedúnculo cerebeloso caudal derecho, DV -7.1 mm, durante un periodo de tiempo de 2 min por medio de una jeringa y aguja Hamilton de µl. Alternativamente se hacen inyecciones en la médula espinal, el cuerpo calloso, o la corteza.
7. La aguja se deja en posición durante los 2 min subsiguientes.
8. Después de la retirada de la aguja se sutura la incisión.
9. Cada rata recibe una inyección i.m. de 0,003 mg de buprenorfina en una pata trasera.
10. La rata se coloca en un armario calentador hasta que recobra el conocimiento. Momento en el cual es devuelta a su jaula. No se permiten más de 2 ratas por jaula, ya que se arrancarán la sutura unas a otras.
11. También se hacen procedimientos similares utilizando ratones.

20 Modelo de Enfermedad de la Encefalomielitis Alérgica Experimental en Rata (EAE en Rata):

La encefalomielitis alérgica experimental (EAE) es una enfermedad autoinmunitaria mediada por células T del sistema nervioso que se desarrolla en animales susceptibles después de la sensibilización o con tejido homogeneizado de médula espinal entera o con un componente (proteína básica de mielina). El modelo de roedor de la EAE es una herramienta apropiada para estudiar la inflamación del cerebro y la médula espinal observada en pacientes de MS. En los roedores, la inyección de médula espinal entera o de componentes de la médula espinal tal como la proteína básica de mielina induce una respuesta autoinmunitaria basada en la activación de los linfocitos T. La enfermedad clínica típicamente llega a ser manifiesta alrededor del día 8-10 después de la inoculación, se observa como un amplio espectro de anomalías conductuales que se extienden

desde leves trastornos de la marcha y atonía de la cola a parálisis completa y muerte. Típicamente tiene lugar una pérdida de peso. En los animales que sobreviven, tiene lugar la recuperación espontánea, acompañada por la recuperación variable de la mayor parte de la función motora. Dependiendo de las especies, el alérgeno, y la metodología utilizada, los animales probados en el modelo EAE pueden experimentar un único ataque (EAE aguda) o varios ataques (EAE recurrente crónica). Se pueden utilizar varios paradigmas de tratamiento: el fármaco o tratamiento de elección se puede administrar antes de la inmunización, durante el periodo no sintomático o durante la enfermedad clínica.

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Animales:

Ratas hembra Lewis, 160-220 g (Charles River)

Antígeno:

Médula espinal entera de Cobaya (Harlan Biosciences).

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Adyuvante de Freund Completo H37 Ra [1 mg/ml Mycobacterium Tuberculosis H37 Ra] (Difco).

Antígeno adicional:

Mycobacterium Tuberculosis (Difco).

Bordetella Pertussis [muerta por calor] (Difco).

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Preparación del antígeno:(para aproximadamente 720 animales):

1. Pesar 5 gramos de médula espinal congelada de cobaya.
2. Añadir 5 g de médula espinal a 5 ml de solución salina al 0,9% (1 g/ml) en un tubo de centrifuga de fondo redondo.
3. Homogeneizar sobre hielo con el Tissue-tech hasta que el tejido esté completamente
- 25 diagregado (aproximadamente 5 minutos).
4. Añadir 10 ml de adyuvante de Freund Completo H37 Ra suplementado con 200 mg de Mycobacterium Tuberculosis (20 mg/ml de adyuvante de Freund Completo H37 Ra).
5. Extraer el homogeneizado / adyuvante del tubo succionándolo con una jeringa de 10
- 30 ml provista con una aguja emulsionante de calibre 18.
6. Emulsionar entre dos jeringas de vidrio de 30 ml hasta que llegue a ser difícil continuar pasando el material a través de la aguja. (Aproximadamente 5 minutos {no de-

be haber ninguna separación entre la fase aceitosa y la fase acuosa)).

7. Utilizar inmediatamente o mantener sobre hielo hasta que se necesite (no más de 30 min) (no congelar).

5

Protocolo

1. Se da libre acceso a la comida y el agua a ratas hembras de Lewis (Charles River) y se deben aclimatar un mínimo de 3 días antes de su uso en los experimentos.
2. Ratas que pesan 160 y 220 gramos son inicialmente provocadas con isoflurano al 5% (Aerrane, Fort Dodge), O₂ al 30%, N₂O al 70% durante 2-5 minutos.
- 10 3. A continuación se pone la rata sobre una manta caliente de agua circulante (Gaymar) (superficie dorsal hacia arriba) y se pone el cono nasal para la respiración espontánea de gases anestésicos. El isoflurano se reduce al 2%.
4. Se hacen dos inyecciones subcutáneas (0,1 ml cada una) o de antígeno o de solución salina isotónica en la superficie ventral de las patas traseras.
- 15 5. A los animales se les quita el cono nasal, se pesan y se numeran.
6. Se permite que las ratas despierten de la anestesia y se ponen en jaulas individuales.
7. Se observa a los animales diariamente buscando signos de la inducción de la EAE (véanse los criterios más abajo).

20	FASE: 0	NORMAL
	FASE: 1	Marcha anormal y atonía de la cola
	FASE: 2	Debilidad leve pero clara de una o ambas patas traseras
	FASE: 3	Debilidad grave de una o ambas patas traseras o ataxia leve
	FASE: 4	Parálisis grave y movimiento mínimo de las patas traseras
25	FASE: 5	Ningún movimiento en las patas traseras y paraplejia
	FASE: 6	Estado moribundo sin ningún movimiento espontáneo y deficiencia respiratoria.
		También puede ocurrir el grado creciente de implicación de las patas delanteras e incontinencia urinaria y fecal
30	FASE: 7	MUERTE

Se comienza el tratamiento en el día 10 después de la inmunización. Puesto que los síntomas de la enfermedad en este modelo aparecen típicamente a los 10-11 días

después de la inoculación, el tiempo señalado puede considerarse que representa la fase inicial de un episodio agudo de MS. Se juzga que este retraso del comienzo del tratamiento imita la situación clínica más estrechamente que los protocolos tradicionalmente utilizados en los que los fármacos se administran a la vez, o incluso antes, que la inoculación (Teitelbaum D. et al., Proc Natl Acad Sci USA 1999; 96: 3842-3847 y Brod S. A., et al., Ann Neurol 2000; 47: 127-131).

Esta invención se ilustra adicionalmente mediante los ejemplos siguientes de compuestos utilizados en la presente memoria que se proporcionan con propósitos de ilustración y en ninguna manera limitan el alcance de la presente invención.

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Ejemplos Sintéticos

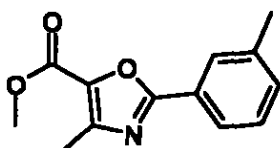
General

Se utilizaron reactivos y disolventes comerciales según se recibieron. Los espectros de RMN ^1H se registraron en un espectrómetro Varian MercuryPlus-300 (300 MHz) o Varian Unity Inova (400 MHz) según se indica. Los desplazamientos químicos de protón se comunican en δ ppm relativo al tetrametilsilano interno (0,0 ppm). Los datos de MS (LC-MS) se obtienen utilizando un espectrómetro de masas de tiempo de vuelo Micromass LCT con ionización por electropulverización y tiempo de adquisición de datos de 5 min para m/z 100 a 1000. La LC (LC-MS) se lleva a cabo utilizando una columna Hypersil C18 (4,6x50mm, 3,5 μ) con fase móvil de TFA al 0,1% en H_2O (A) y TFA al 0,1% en ACN (B) y un gradiente de 5% a 100% de B durante un periodo de 3 min seguido por 2 min a 100% de B. Alternativamente, se puede utilizar una Plataforma de LC-MS con una fuente de electropulverización con un sistema de LC HP1100 funcionando a 2,0 ml/min, división de flujo de 200 $\mu\text{L}/\text{min}$ a la fuente de ESI con detección DAD HP1100 en línea y detección ELS SEDEX. Se utiliza una columna Luna C18(2) (30x4,6mm 3 μ) gradiente de 5% a 95% B durante un periodo de 4,5 min con fase móvil de ácido fórmico al 0,1% en H_2O y ácido fórmico al 0,1% en ACN (B). La purificación por HPLC se lleva a cabo en un sistema ProStar de Varian utilizando una columna de C18 de fase inversa con un gradiente lineal de ACN / H_2O que contiene ácido trifluoroacético al 0,1%. Las síntesis con microondas se llevaron a cabo utilizando un sistema de reacción de microondas Personal Chemistry Smithcreator que utiliza recipientes del re-

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actor de 2 o 5 mL.

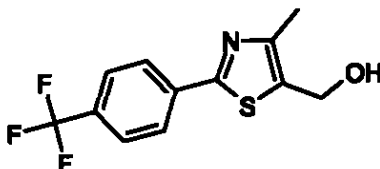
Ejemplo 1



Producto intermedio: Éster metílico del ácido 4-metil-2-*m*-tolil-oxazol-5-carboxílico

Calentar a 120°C una mezcla pura de 2-cloroacetoacetato de metilo (914 mL, 7,5 mmol) y 3-metil-benzamida (676 mg, 5 mmol) y agitar a esta temperatura durante 12
10 hors. Enfriar la mezcla de reacción a temperatura ambiente y diluir la con acetato de etilo, lavar con disolución saturada de bicarbonato sódico (3 veces), agua (dos veces) y salmuera. Secar el extracto orgánico sobre MgSO₄ y concentrar. Purificar el residuo resultante por cromatografía instantánea ("flash") (eluir con acetato de etilo al 10% en
15 heptano) para dar el compuesto del título como un aceite amarillo (492 mg).

Ejemplo 2



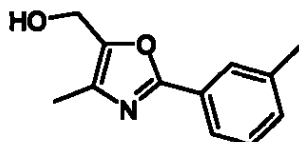
Producto intermedio: [4-Metil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol

Enfriar (0°C) una disolución de hidruro de litio y aluminio (10 mL, 1M en THF) y añadir una disolución de ácido 4-metil-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico
25 (disponible comercialmente, 2,87g, 10 mmol) en THF (20 mL). Al completar la adición, quitar el baño frío y agitar durante 3,5 horas. Enfriar esta disolución a 5°C, y a continuación añadir agua (0,25 mL), gota a gota, seguido por disolución de NaOH (0,25 mL, 5M

en agua) y agua (0,5 mL). Diluir la mezcla resultante con acetato de etilo y después filtrar a través de un lecho de celita. Lavar los sólidos con diclorometano y después concentrar los filtrados combinados a presión reducida para dar el compuesto del título como un sólido amarillo (2,59 g).

- 5 MS (ESI) m/z 274 (M+H); RMN H1 (CDCl₃) δ 1,87 (s ancho, 1H), 2,49 (s, 3H), 4,86 (s, 2H), 7,67 (d, J = 8Hz, 2H), 8,02 (d, J = 8Hz, 2H).

Ejemplo 3



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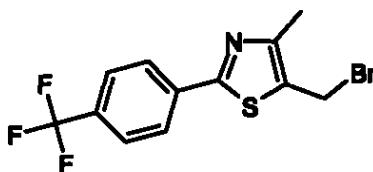
Producto intermedio: [4-Metil-2-*m*-tolil-oxazol-5-il]-metanol

- 15 Seguir el procedimiento del Ejemplo 2, pero utilizar el compuesto del Ejemplo 1 como el producto de partida para obtener el compuesto del título.

MS (ESI) m/z 204 (M+H); RMN H1 (CDCl₃) δ 2,25 (s, 3H), 2,40 (t, J = 7Hz, 1H), 2,42 (s, 3H), 4,70 (d, J = 7Hz, 2H), 7,25-7,36 (m, 2H), 7,75-7,85 (m, 2H).

Ejemplo 4

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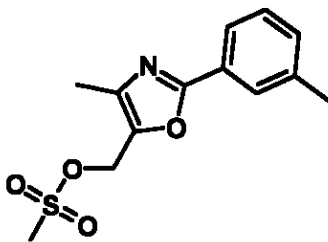
Producto intermedio: 5-Bromometil-4-metil-2-(4-trifluorometil-fenil)-tiazol

- 25 Enfriar (10°C) una disolución de [4-metil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol (Ejemplo 2, 753 mg, 3 mmol) en THF (12 mL) añadir trifenilfosfina (864 mg, 3,3 mmol) seguido por *N*-bromosuccinimida (587 mg, 3,3 mmol) recientemente recris-

talizada. Al completar la adición, quitar el baño frío y agitar continuamente durante 45 min. Concentrar la mezcla resultante a vacío y purificar el residuo por cromatografía instantánea (eluir con acetato de etilo al 10% / diclorometano al 10% en heptano) para dar el compuesto del título como un sólido naranja (846 mg).

- 5 MS (ESI) m/z 336, 338 (M+H); RMN H1 (CDCl₃) δ 2,48 (s, 3H), 4,72 (s, 2H), 7,69 (d, J = 8Hz, 2H), 8,01 (d, J = 8Hz, 2H).

Ejemplo 5

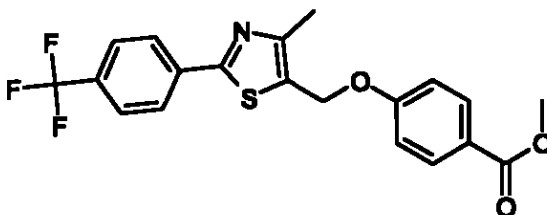


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Producto intermedio: Éster de [2-(3-metil-fenil)-4-metil oxazol-5-il]-metilo del ácido metanosulfónico

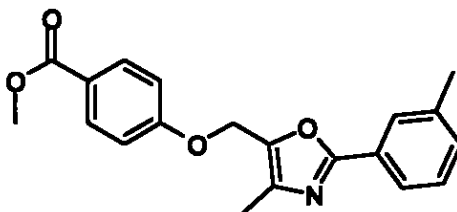
- 15 Enfriar (0°C) una disolución de [2-(3-metil-fenil)-4-metil oxazol-5-il]-metanol (Ejemplo 3, 756 mg, 4 mmol) en diclorometano (16 mL) y añadir, secuencialmente, DMAP (51 mg, 0,4 mmol), trietilamina (552 μ L, 4 mmol) y cloruro de metanosulfonilo (323 μ L, 4,2 mmol). Agitar la disolución resultante durante 5 minutos, quitar el baño refrigerante y agitar durante 25 min. Diluir esta disolución con éter, lavar con ácido
- 20 clorhídrico (5 mL, 2M), salmuera, secar sobre MgSO₄ y concentrar para dar el compuesto del título (743 mg).

Ejemplo 6



5 **Producto intermedio: Éster metílico del ácido 4-[4-metil-2-(4-trifluorometil-fenil)-
thiazol-5-ilmetoxi]-benzoico**

- A una mezcla de éster metílico del ácido 4-hidroxibenzoico (152 mg, 1 mmol) y carbonato potásico (152 mg, 1,1 mmol) añadir acetonitrilo (4 mL). Añadir a esta mezcla
- 10 5-bromometil-4-metil-2-(4-trifluorometil-fenil)-thiazol (Ejemplo 4, 314 mg, 1 mmol). Calentar la mezcla de reacción resultante a 60°C, y agitar a esta temperatura durante 5 horas. Enfriar la mezcla a temperatura ambiente, diluir con acetato de etilo, lavar con agua, después con salmuera, secar sobre MgSO₄, filtrar y concentrar para dar el compuesto del título como un sólido blanco (364 mg).
- 15 MS (ESI) *m/z* 408 (M+H); RMN H¹ (CDCl₃) δ 2,53 (s, 3H), 3,90 (s, 3H), 4,52 (s, 2H), 7,00 (d, *J* = 9Hz, 2H), 7,68 (d, *J* = 8Hz, 2H), 8,02 (m, 4H).

Ejemplo 7

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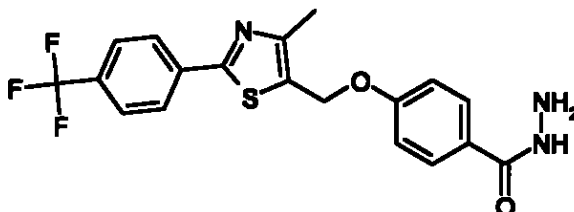
**Producto intermedio: Éster metílico del ácido 4-(4-metil-2-*m*-tolil-oxazol-5-ilmetoxi)-
benzoico**

- Seguir el procedimiento del Ejemplo 6, pero utilizar el compuesto del Ejemplo 5
- 25 como el producto de partida para obtener el compuesto del título.

MS (ESI) m/z 338 (M+H); RMN H1 (CDCl₃) δ 2,30 (s, 3H), 2,41 (s, 3H), 3,90 (s, 3H), 5,11 (s, 2H), 7,03 (d, J = 9Hz, 2H), 7,25 (m, 1H), 7,33 (t, J = 8Hz, 1H), 7,81 (d, J = 8Hz, 1H) 7,87 (s ancho, 1H) 8,02 (d, J = 9Hz, 2H).

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Ejemplo 8



Producto intermedio: Hidracida del ácido 4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-benzoico

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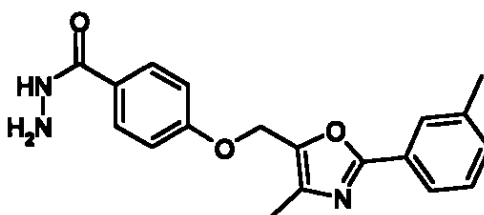
A una suspensión de éster metílico del ácido 4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-benzoico (Ejemplo 6, 364 mg, 1 mmol) en metanol (10 mL) añadir hidracina anhidra (128 ml, 4 mmol). Calentar la mezcla resultante a 60°C y agitar a esta temperatura durante 18 horas. Enfriar la disolución resultante a temperatura ambiente, y añadir 3 gotas de agua. Concentrar la disolución a vacío y purificar el residuo por cromatografía instantánea (eluir con metanol al 5% en diclorometano) para dar el compuesto del título (271 mg).

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MS (ESI) m/z 408 (M+H); RMN H1 (DMSO) δ 2,51 (s, 3H), 4,4 (s ancho, 2H), 5,42 (s, 2H) 7,10 (d, J = 9Hz, 2H), 7,82 (d, J = 9Hz, 2H), 7,85 (d, J = 8Hz, 2H) 8,12 (d, J = 8Hz, 2H) 9,63 (s ancho, 1H).

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Ejemplo 9



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Producto intermedio: Hidracida del ácido 4-(4-metil-2-*m*-tolil-oxazol-5-ilmetoxi)-benzoico

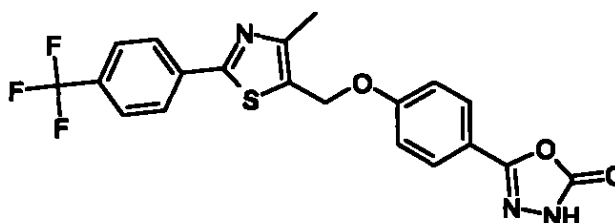
Seguir el procedimiento del Ejemplo 8, pero utilizar el compuesto del Ejemplo 7 como el producto de partida para obtener el compuesto del título.

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MS (ESI) m/z 338 (M+H); RMN H1 (DMSO) δ 2,24 (s, 3H), 2,38 (s, 3H), 4,43 (s ancho, 2H), 5,26 (s, 2H) 7,11 (d, $J = 9\text{Hz}$, 2H), 7,34 (d, $J = 8\text{Hz}$, 1H), 7,41 (t, $J = 8\text{Hz}$, 1H) 7,74-7,83 (m, 4H) 9,63 (s ancho, 1H).

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Ejemplo 10



5-{4-[4-Metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-3H-[1,3,4]oxadiazol-2-ona

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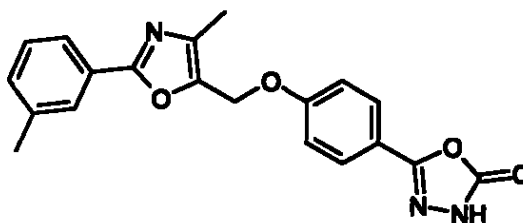
A una suspensión de hidracida del ácido 4-[4-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-benzoico (Ejemplo 8, 271 mg, 0,74 mmol) en diclorometano (7 mL) añadir cloroformiato de fenilo (94 μL , 0,75 mmol) seguido por piridina (132 μL , 1,63 mmol). Agitar la mezcla resultante a temperatura ambiente hasta que se consuma todo el

25

producto de partida (por análisis de TLC). Concentrar la mezcla, y a continuación recoger el residuo en acetonitrilo (10 mL). A esta mezcla, añadir DBU (220 μ L, 1,5 mmol). Sellar la disolución resultante; calentarla a 180°C en un horno microondas Personal Chemistry™ y agitar a esta temperatura durante 15 minutos. Enfriar la reacción a temperatura ambiente, diluir con acetato de etilo, lavar con disolución de HCl 1 M (o disolución saturada de NaH₂PO₄) secar sobre MgSO₄ y concentrar. Triturar el residuo resultante con diclorometano varias veces para dar el compuesto del título como un sólido color canela (69 mg).

MS (ESI) m/z 365 (M+H); RMN H1 (DMSO) δ 2,51 (s, 3H), 4,4 (s ancho, 2H), 5,42 (s, 2H) 7,10 (d, J = 9Hz, 2H), 7,82 (d, J = 9Hz, 2H), 7,85 (d, J = 8Hz, 2H) 8,12 (d, J = 8Hz, 2H) 9,63 (s ancho, 1H).

Ejemplo 11

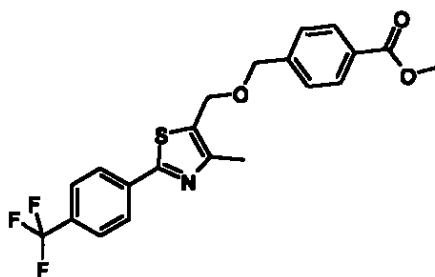


5-[4-(4-Metil-2-m-tolil-oxazol-5-il)metoxi]-fenil]-3H-[1,3,4]oxadiazol-2-ona.

Seguir el procedimiento del Ejemplo 10, pero utilizar el compuesto del Ejemplo 9 como el producto de partida para obtener el compuesto del título.

MS (ESI) m/z 364 (M+H); RMN H1 (DMSO) δ 2,25 (s, 3H), 2,38 (s, 3H), 5,30 (s, 2H) 7,23 (d, J = 9Hz, 2H), 7,34 (d, J = 8Hz, 1H), 7,41 (t, J = 8Hz, 1H) 7,75-7,79 (m, 4H) 12,44 (s ancho, 1H).

Ejemplo 12



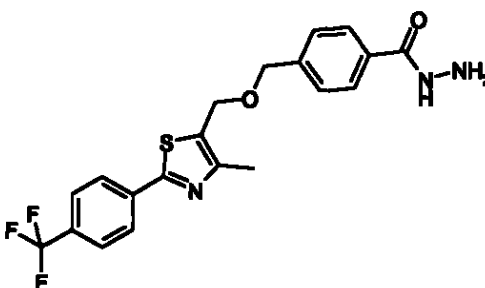
5 **Producto intermedio: Éster metílico del ácido 4-([4-metil-2-(4-trifluorometil-fenil)-tiazol-5-il)-metoximetil]-benzoico**

Enfriar (-5°C) una suspensión de NaH (84mg, 60% dispersión en aceite mineral,
 10 2,05 mmol) en THF (4 mL) y añadir una disolución que consiste en 2-([4-metil-2-(4-trifluorometil-fenil)-tiazol-5-il)-metanol (546 mg, 2 mmol) y éster metílico del ácido 4-bromometil-benzoico (458 mg, 2 mmol) en THF (5 mL). Agitar la mezcla resultante durante 5 minutos después quitar el baño frío y agitar durante 3 horas adicionales. Parar la reacción con disolución de HCl 1M, diluir con acetato de etilo, lavar con salmuera y
 15 secar sobre MgSO₄. Concentrar esta disolución a vacío y purificar el residuo por cromatografía instantánea (eluyendo con acetato de etilo al 20% en heptano) para dar el producto (377 mg) como un sólido blanco.

MS (ESI) *m/z* 422 (M+H); RMN H1 (CDCl₃) δ 2,44 (s, 3H), 3,92 (s, 3H), 4,64 (s, 2H), 4,71 (s, 2H), 7,42 (d, *J* = 8Hz, 2H), 7,66 (d, *J* = 8Hz, 2H) 8,00 (m, 4H).

20

Ejemplo 13



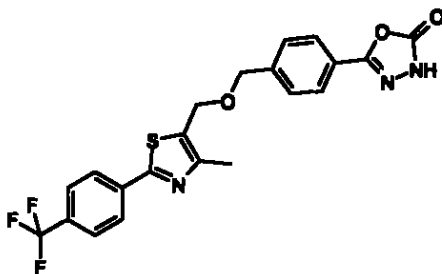
Producto intermedio: Hidracida del ácido 4-([4-metil-2-(4-trifluorometil-fenil)-tiazol-5-il)-metoximetil]-benzoico

Seguir el procedimiento del Ejemplo 8, pero utilizar el compuesto del Ejemplo 12 como el producto de partida para obtener el compuesto del título.

MS (ESI) m/z 422 (M+H); RMN H1 (CDCl₃) δ 2,44 (s, 3H), 4,09 (s ancho, 2H), 4,63 (s, 2H), 4,71 (s, 2H), 7,30 (s ancho, 1H), 7,44 (d, $J = 8\text{Hz}$, 2H), 7,66 (d, $J = 8\text{Hz}$, 2H), 7,73 (d, $J = 8\text{Hz}$, 2H) 8,00 (d, $J = 8\text{Hz}$, 2H).

10

Ejemplo 14



5-(4-[4-Metil-2-(4-trifluorometil-fenil)-tiazol-5-il)-metoximetil]-fenil}-3H-[1,3,4]oxadiazol-2-ona

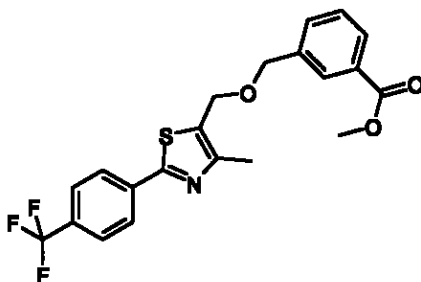
15

Seguir el procedimiento del Ejemplo 10, pero utilizar el compuesto del Ejemplo 13 como el producto de partida para obtener el compuesto del título.

MS (ESI) m/z 448 (M+H); RMN H1 (DMSO) δ 2,40 (s, 3H), 4,65 (s, 2H), 4,78 (s, 2H) 7,50 (d, $J = 8\text{Hz}$, 2H), 7,78 (d, $J = 8\text{Hz}$, 2H), 7,82 (d, $J = 8\text{Hz}$, 2H) 8,10 (d, $J = 8\text{Hz}$, 2H) 12,54 (s ancho, 1H).

20

Ejemplo 15

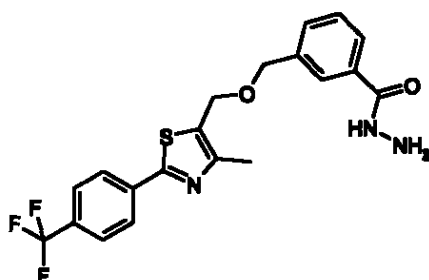


5 **Producto intermedio: Éster metílico del ácido 4-([3-metil-2-(4-trifluorometil-fenil)-**
tiazol-5-il)-metoximetil]-benzoico

Enfriar (0°C) una disolución de 2-([4-metil-2-(4-trifluorometil-fenil)-tiazol-5-il)-
 metanol (450 mg, 1,64 mmol) en THF y añadir NaH (70mg, dispersión en aceite mine-
 10 ral al 50%, 1,75 mmol). Agitar la mezcla resultante durante 5 min. Quitar el baño frío y
 continuar agitando durante 1 hora. A esta mezcla añadir éster metílico del ácido 3-
 (bromometil)-benzoico (450mg, 1,95 mmol). Agitar la mezcla resultante durante 3
 horas y a continuación parar la reacción con disolución saturada de NH₄Cl. Diluir la
 mezcla con éter, lavar con salmuera, secar sobre MgSO₄ y concentrar a vacío. Purificar
 15 el residuo por cromatografía instantánea (eluyendo con acetato de etilo al 30% en hep-
 tano) para dar el compuesto del título (181 mg) como un aceite.

MS (ESI) *m/z* 422 (M+H); RMN H1 (CDCl₃) δ 2,44 (s, 3H), 3,92 (s, 3H), 4,63 (s, 2H),
 4,71 (s, 2H) 7,44 (t, *J* = 8Hz, 1H), 7,56 (d, *J* = 8Hz, 1H), 7,66 (d, *J* = 8Hz, 2H)), 7,00
 (m, 4H).

Ejemplo 16

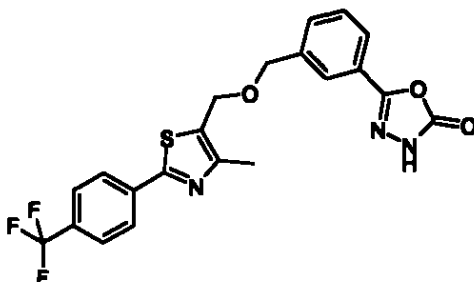


5 Producto intermedio: Hidracida del ácido 4-([3-metil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metoximetil)-benzoico

Seguir el procedimiento del Ejemplo 8, pero utilizar el compuesto del Ejemplo 15 como el producto de partida para obtener el compuesto del título.

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Ejemplo 17

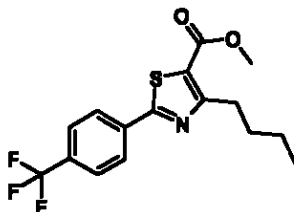


15 5-([3-[4-Metil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metoximetil]-fenil)-3H-[1,3,4]oxadiazol-2-ona

Seguir el procedimiento del Ejemplo 10, pero utilizar el compuesto del Ejemplo 16 como el producto de partida para obtener el compuesto del título.

20 MS (ESI) m/z 448 (M+H); RMN H1 (DMSO) δ 2,40 (s, 3H), 4,65 (s, 2H), 4,79 (s, 2H) 7,53 (m, 2H), 7,72 (m, 1H), 7,77 (s, 1H), 7,82 (d, J = 8Hz, 2H), 8,10 (d, J = 8Hz, 2H), 12,5 (s ancho, 1H).

Ejemplo 18

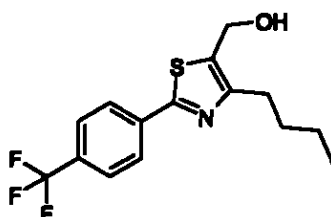


5

Producto intermedio: Éster metílico del ácido 4-butil-2-(4-trifluorometil-fenil)-tiazol-5-carboxílico

- 10 A una disolución de éster metílico del ácido 3-oxo-heptanoico (5,0 g, 31,6 mmol) en diclorometano seco (80 mL) añadir cloruro de sulfurilo (2,82 mL). Agitar la mezcla de reacción a temperatura ambiente durante 30 minutos a continuación añadir agua (20 mL) y la mezcla de reacción se extrae cinco veces con porciones de 30 mL de diclorometano. Lavar los extractos orgánicos combinados con agua, disolución acuosa saturada de NaHCO₃ y salmuera y después secar sobre MgSO₄. Eliminar el disolvente a presión reducida para dar el éster metílico del ácido 2-cloro-3-oxo-heptanoico (6,0 g),
- 15 que se utilizó en la etapa siguiente sin purificación adicional. A una disolución de éster metílico del ácido 2-cloro-3-oxo-heptanoico (6,0 g, 31,1 mmol) en etanol (50 mL) añadir 4-(trifluorometil) tiobenzamida (6,4 g, 31,2 mmol). Calentar la mezcla de reacción a reflujo durante toda la noche. Eliminar el disolvente a presión reducida y purificar el
- 20 residuo por cromatografía en gel de sílice (eluyendo con un gradiente de n-heptano:acetato de etilo (100:1 a 60:1)) para dar el éster metílico del ácido 4-butil-2-(4-trifluorometil-fenil)-tiazol-5- carboxílico (7,4 g) como un aceite amarillo.
- MS (ESI) m/z 344 (M+H).

Ejemplo 19



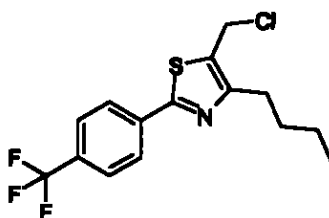
5 Producto intermedio: [4-Butil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol

A una disolución de hidruro de litio y aluminio (1,2 g) en tetrahidrofurano seco (100 mL) añadir éster metílico del ácido 4-butil-2-(4-trifluorometil-fenil)-tiazol-5- carboxílico (5,3 g, 15,4 mmol) disuelto en tetrahidrofurano (100 mL). Agitar la mezcla de
10 reacción a temperatura ambiente durante un periodo de una hora. Añadir una disolución acuosa saturada de cloruro amónico (50 mL) y a continuación una disolución acuosa de ácido clorhídrico 1 molar (50 mL). Extraer la mezcla de reacción cinco veces con porciones de 60 ml de acetato de etilo. Secar los extractos combinados con MgSO₄ y eliminar el disolvente a presión reducida para proporcionar [4-butil-2-(4-trifluorometil-fenil)-
15 tiazol-5-il]-metanol (4,6 g) como un aceite amarillo, que solidifica tras dejarlo estar a temperatura ambiente.

MS (ESI) *m/z* 316 (M+H); RMN H1 (DMSO-d₆) δ 0,91 (t, *J* = 7,0 Hz, 3H), 1,35 (m, 2H), 1,64 (m, 2H), 2,70 (m, 2H), 4,68 (m ancho, 2H), 5,63 (m ancho, 1H), 7,83 (d ancho, *J* = 8,5 Hz, 2H), 8,09 (d ancho, *J* = 8,5 Hz, 2H).

20

Ejemplo 20



25 Producto intermedio: 4-Butil-5-clorometil-2-(4-trifluorometil-fenil)-tiazol

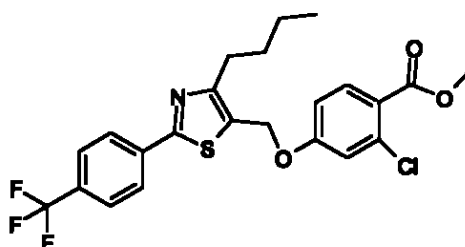
A una disolución de [4-butil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol (1,0

g, 3,1 mmol) en diclorometano (50 mL) añadir trietilamina (0,88 mL) y cloruro de metanosulfonilo (0,39 mL). Agitar la mezcla de reacción a temperatura ambiente durante un periodo de tres horas y después añadir diclorometano (100 mL). Lavar la mezcla de reacción con una disolución acuosa saturada de NaHCO_3 (50 mL), agua y salmuera. Secar la capa orgánica sobre MgSO_4 y eliminar el disolvente a presión reducida para dar 4-butil-5-clorometil-2-(4-trifluorometil-fenil)-tiazol (1,0 g) como un aceite amarillo.

MS (ESI) m/z 334 (M+H); RMN ^1H ($\text{DMSO}-d_6$) δ 0,92 (t, $J = 7,5$ Hz, 3H), 1,37 (m, 2H), 1,68 (m, 2H), 2,80 (m, 2H), 5,14 (s, 2H), 7,86 (d ancho, $J = 8,5$ Hz, 2H), 8,12 (d ancho, $J = 8,5$ Hz, 2H).

10

Ejemplo 21



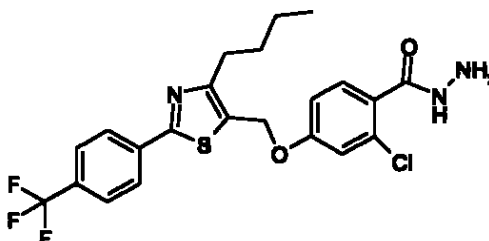
15 Producto intermedio: Éster metílico del ácido 4-[4-butil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-cloro-benzoico

A una disolución enfriada en hielo de [4-butil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol (1,0 g, 3,17 mmol), éster metílico del ácido 2-cloro-4-hidroxi-benzoico (592 mg, 3,17 mmol) y trifenilfosfina (832 mg, 3,17 mmol) en diclorometano añadir azodicarboxilato de dietilo (0,567 mL, 3,17 mmol). Agitar la mezcla de reacción durante 2 horas mientras que se la deja calentar a temperatura ambiente. Eliminar el disolvente a presión reducida y purificar el residuo por cromatografía instantánea sobre gel de sílice para dar éster metílico del ácido 4-[4-butil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-cloro-benzoico (600 mg).

25

MS (ESI) m/z 484 (M+H).

Ejemplo 22

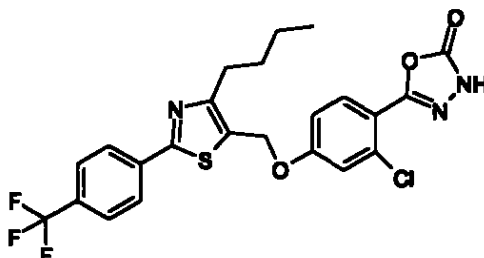


5 Producto intermedio: Hidracida del ácido 4-[4-butil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-cloro-benzoico

Seguir el procedimiento del Ejemplo 8, pero utilizar el compuesto del Ejemplo 21 como el producto de partida para obtener el compuesto del título.

10 MS (ESI) m/z 484 (M+H).

Ejemplo 23



15

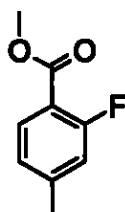
5-[4-[4-Butil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-2-cloro-fenil]-3H-[1,3,4]oxadiazol-2-ona

20 Seguir el procedimiento del Ejemplo 10, pero utilizar el compuesto del Ejemplo 22 como el producto de partida para obtener el compuesto del título.

MS (ESI) m/z 510 (M+H); RMN H1 (DMSO-d6) δ 0,91 (t, 3H), 1,37 (m, 2H), 1,68 (m, 2H), 2,83 (t, 2H), 5,50 (s, 2H), 7,19 (dd, $J = 9, 2,5$ Hz, 1H), 7,40 (d, $J = 2,4$ Hz, 1H), 7,77 (d, $J = 8,6$ Hz, 1H), 7,86 (d, $J = 8,0$ Hz, 2H), 8,13 (d, $J = 8,3$ Hz, 2H), 12,64 (s ancho, 1H).

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Ejemplo 24



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Producto intermedio: Éster metílico del ácido 2-fluoro-4-metil-benzoico

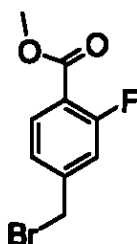
A una disolución de ácido 2-fluoro-4-metil-benzoico (1,1 g, 7,13 mmol) en metanol (20 mL) añadir cloruro de tionilo (1,02 g, 8,56 mmol). Agitar la mezcla resultante durante toda la noche y a continuación concentrar a vacío para dar el compuesto del título (1,2 g) como un sólido blanco.

10

MS (ESI) m/z 169 (M+H); RMN H1 (DMSO- d_6) δ 2,37 (s, 3H), 3,83 (s, 3H), 7,12-7,21 (m, 2H), 7,79 (t, J = 8,0 Hz, 1H).

15

Ejemplo 25



Producto intermedio: Éster metílico del ácido 4-bromometil-2-fluoro-benzoico

A una disolución de éster metílico del ácido 2-fluoro-4-metil-benzoico (1,12 g, 6,66 mmol) en tetracloruro de carbono (12 mL) añadir N-bromosuccinimida (1,18 g, 6,66 mmol) y peróxido de benzoilo (10 mg). Calentar la mezcla resultante a 60°C durante 15 horas y a continuación concentrar a vacío a la mitad y filtrar. Concentrar el filtrado a vacío y purificar el producto bruto resultante por cromatografía instantánea sobre gel de sílice (eluyendo con heptano/acetato de etilo 5/1) para dar el compuesto del título

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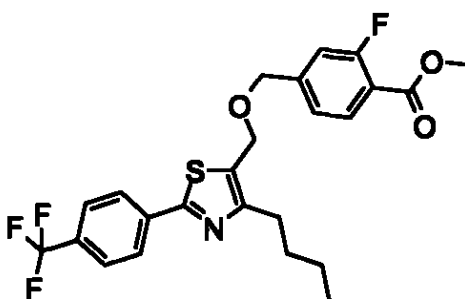
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(1,35 g) como un sólido blanco.

MS (ESI) m/z 247 (M+H); RMN H1 (DMSO- d_6) δ 3,85 (s, 3H), 4,73 (s, 2H), 7,37-7,48 (m, 2H), 7,88 (t, J = 8,0 Hz, 1H).

5

Ejemplo 26



Producto intermedio: Éster metílico del ácido 4-[4-Butil-2-(4-trifluorometil-fenil)-
tiazol-5-ilmetoximetil]-2-fluoro-benzoico

10

A una disolución de [4-butil-2-(4-trifluorometil-fenil)-tiazol-5-il]-metanol (1,02 g, 3,24 mmol) en DMF anhidra (150 mL) añadir carbonato de cesio (2,7 g, 8,10 mmol) y éster metílico del ácido 4-bromometil-2-fluoro-benzoico (0,8 g, 3,24 mmol). Agitar la mezcla resultante durante toda la noche a continuación verter en una disolución acuosa de hidrogenofosfato potásico 1M y se extrae tres veces con éter diisopropílico. Lavar los extractos combinados con agua, secar sobre $MgSO_4$, filtrar y concentrar a vacío. Purificar el residuo por cromatografía instantánea sobre gel de sílice (eluyendo con un gradiente de heptano/acetato de etilo) para dar el compuesto del título (0,3 g) como un sólido amarillo.

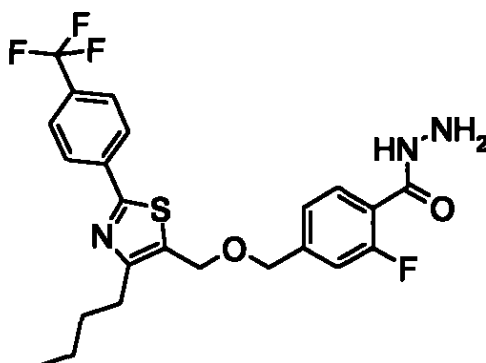
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MS (ESI) m/z 482 (M+H); RMN H1 (DMSO- d_6) δ 0,89 (t, J = 7,5 Hz, 3H), 1,33 (m, 2H), 1,65 (m, 2H), 2,72 (m, 2H), 3,86 (s, 3H), 4,67 (s, 2H), 4,80 (s, 2H), 7,28-7,34 (m, 2H), 7,86 (d ancho, J = 8,5 Hz, 2H), 7,90 (t, J = 8,0 Hz, 1H), 8,11 (d ancho, J = 8,5 Hz, 2H).

25

Ejemplo 27



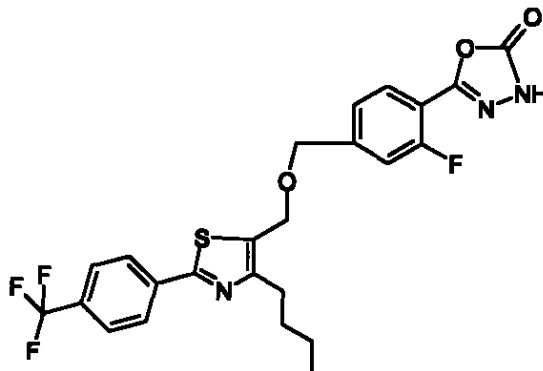
5 Producto intermedio: Hidracida del ácido 4-[4-Butil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoximetil]-2-fluoro-benzoico

Seguir el procedimiento del Ejemplo 8, pero utilizar el compuesto del Ejemplo 26 como el producto de partida para obtener el compuesto del título.

10 MS (ESI) m/z 482 (M+H); RMN H1 (DMSO- d_6) δ 0,90 (t, $J = 7,5$ Hz, 3H), 1,33 (m, 2H), 1,65 (m, 2H), 2,72 (m, 2H), 4,53 (s ancho, 2H), 4,62 (s, 2H), 4,79 (s, 2H), 7,20-7,29 (m, 2H), 7,57 (t ancho, $J = 8,0$ Hz, 1H), 7,84 (d ancho, $J = 8,5$ Hz, 2H), 8,12 (d ancho, $J = 8,5$ Hz, 2H), 9,51 (m, 1H) .

15

Ejemplo 28

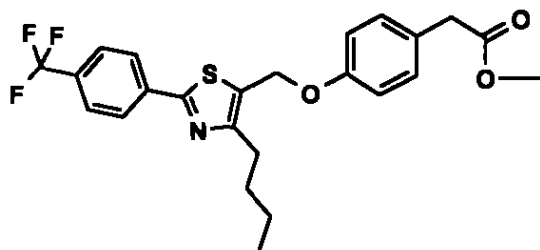


20 5-{4-[4-Butil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoximetil]-2-fluoro-fenil}-3H-[1,3,4]oxadiazol-2-ona

Seguir el procedimiento del Ejemplo 10, pero utilizar el compuesto del Ejemplo 27 como el producto de partida para obtener el compuesto del título.

MS (ESI) m/z 508 (M+H); RMN H1 (DMSO- d_6) δ 0,89 (t, $J = 7,5$ Hz, 3H), 1,33 (m, 2H), 1,65 (m, 2H), 2,73 (m, 2H), 4,68 (s, 2H), 4,81 (s, 2H), 7,33-7,40 (m, 2H), 7,80 (t, $J = 8,0$ Hz, 1H), 7,85 (d ancho, $J = 8,5$ Hz, 2H), 8,12 (d ancho, $J = 8,5$ Hz, 2H), 12,70 (m ancho, 1H).

Ejemplo 29



Producto intermedio: Éster metílico del ácido {4-[4-butil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-acético

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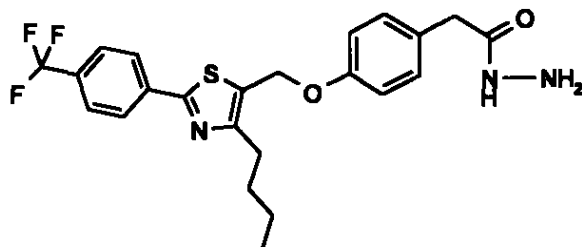
A una disolución de 4-butil-5-clorometil-2-(4-trifluorometil-fenil)-tiazol (278 mg, 0,83 mmol) en DMF anhidra (5 mL) añadir carbonato de cesio (297 mg, 1,66 mmol) y 4-hidroxifenilacetato de metilo (200 mg, 1,20 mmol). Agitar la mezcla resultante durante toda la noche a continuación verter en agua y extraer dos veces con acetato de etilo. Lavar los extractos combinados con agua, secar sobre $MgSO_4$, filtrar y concentrar a vacío para dar el compuesto del título (290 mg) como un sólido amarillento.

20

MS (ESI) m/z 508 (M+H); RMN H1 (DMSO- d_6) δ 0,90 (t, $J = 7,5$ Hz, 3H), 1,36 (m, 2H), 1,67 (m, 2H), 2,80 (m, 2H), 3,60 (s, 3H), 3,61 (s, 2H), 5,33 (s, 2H), 7,00 (d ancho, $J = 8,5$ Hz, 2H), 7,21 (d ancho, $J = 8,5$ Hz, 2H), 7,84 (d ancho, $J = 8,5$ Hz, 2H), 8,12 (d ancho, $J = 8,5$ Hz, 2H).

25

Ejemplo 30



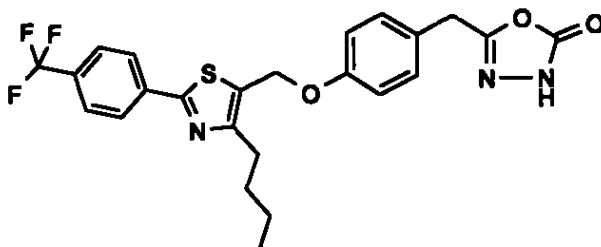
5 Producto intermedio: Hidracida del ácido {4-[4-butil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-acético

Seguir el procedimiento del Ejemplo 8, pero utilizar el compuesto del Ejemplo 29 como el producto de partida para obtener el compuesto del título.

10 MS (ESI) m/z 464 (M+H); RMN ^1H (DMSO- d_6) δ 0,91 (t, $J = 7,5$ Hz, 3H), 1,36 (m, 2H), 1,67 (m, 2H), 2,80 (m, 2H), 3,28 (s, 2H), 4,17 (d ancho, $J = 4,0$ Hz, 2H), 5,32 (s, 2H), 6,97 (d ancho, $J = 8,5$ Hz, 2H), 7,19 (d ancho, $J = 8,5$ Hz, 2H), 7,84 (d ancho, $J = 8,5$ Hz, 2H), 8,12 (d ancho, $J = 8,5$ Hz, 2H), 9,13 (t ancho, $J = 4,0$ Hz, 1H).

15

Ejemplo 31



20 5-{4-[4-Butil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-bencil}-3H-[1,3,4]oxadiazol-2-ona

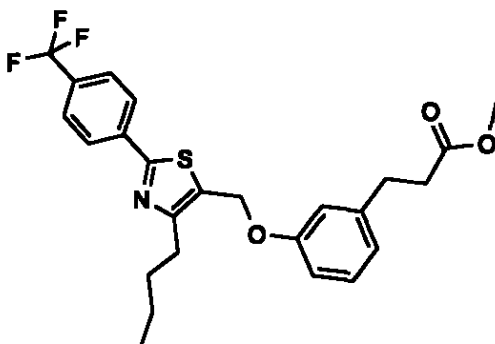
Seguir el procedimiento del Ejemplo 10, pero utilizar el compuesto del Ejemplo 30 como el producto de partida para obtener el compuesto del título.

MS (ESI) m/z 490 (M+H); RMN ^1H (DMSO- d_6) δ 0,90 (t, $J = 7,5$ Hz, 3H), 1,36 (m,

2H), 1,68 (m, 2H), 2,80 (m, 2H), 3,87 (s, 2H), 5,33 (s, 2H), 7,03 (d ancho, $J = 8,5$ Hz, 2H), 7,24 (d ancho, $J = 8,5$ Hz, 2H), 7,85 (d ancho, $J = 8,5$ Hz, 2H), 8,12 (d ancho, $J = 8,5$ Hz, 2H), 11,7-12,4 (m ancho, 1H).

5

Ejemplo 32



Producto intermedio: Éster metílico del ácido 3-(3-[4-butil-2-(4-trifluorometil-fenil)-
tiazol-5-ilmetoxi]-fenil)-propiónico

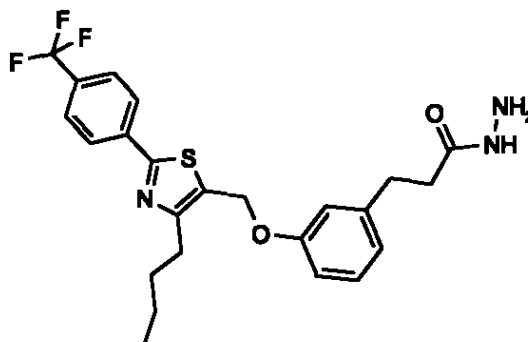
10

A una disolución de 4-butil-5-clorometil-2-(4-trifluorometil-fenil)-tiazol (300 mg, 0,90 mmol) en DMF anhidra (5 mL) añadir carbonato de cesio (586 mg, 1,80 mmol) y 3-(3-hidroxifenil)propionato de metilo (178 mg, 0,99 mmol). Agitar la mezcla resultante durante toda la noche a continuación verter en agua y extraer dos veces con acetato de etilo. Lavar los extractos combinados con agua, secar sobre MgSO_4 , filtrar y concentrar a vacío. Purificar el residuo por cromatografía instantánea sobre gel de sílice (eluyendo con acetato de etilo al 5% en heptano) para dar el compuesto del título (290 mg) como un aceite amarillo.

15

20 MS (ESI) m/z 478 ($\text{M}+\text{H}$); RMN ^1H ($\text{DMSO}-d_6$) δ 0,91 (t, $J = 7,5$ Hz, 3H), 1,37 (m, 2H), 1,68 (m, 2H), 2,64 (m, 2H), 2,76-2,88 (m, 4H), 3,58 (s, 3H), 5,33 (s, 2H), 6,82-6,91 (m, 2H), 6,93 (s ancho, 1H), 7,22 (t, $J = 8,0$ Hz, 1H), 7,85 (d ancho, $J = 8,5$ Hz, 2H), 8,12 (d ancho, $J = 8,5$ Hz, 2H).

Ejemplo 33



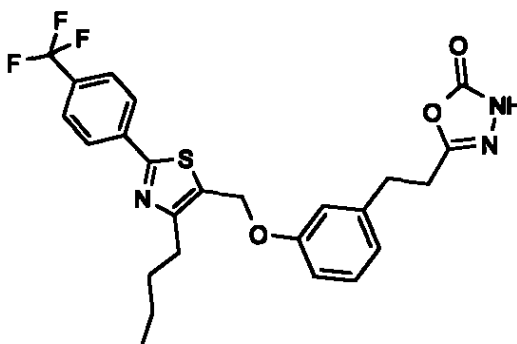
5 Producto intermedio: Hidracida del ácido 3-{3-[4-butil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-propiónico

Seguir el procedimiento del Ejemplo 8, pero utilizar el compuesto del Ejemplo 32 como el producto de partida para obtener el compuesto del título.

10 MS (ESI) m/z 478 (M+H); RMN ^1H (DMSO- d_6) δ 0,91 (t, $J = 7,5$ Hz, 3H), 1,36 (m, 2H), 1,68 (m, 2H), 2,33 (m, 2H), 2,80 (m, 4H), 4,14 (d ancho, $J = 4,0$ Hz, 2H), 5,32 (s, 2H), 6,79-6,92 (m, 3H), 7,21 (t, $J = 7,5$ Hz, 1H), 7,85 (d ancho, $J = 8,5$ Hz, 2H), 8,12 (d ancho, $J = 8,5$ Hz, 2H), 8,94 (m ancho, 1H).

15

Ejemplo 34



20 5-(2-{3-[4-Butil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi]-fenil}-etil)-3H-[1,3,4]oxadiazol-2-ona

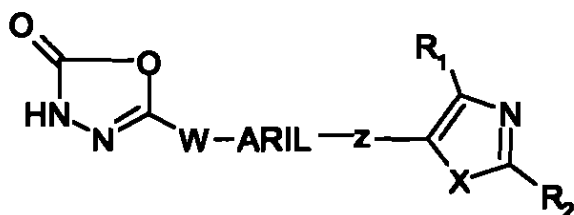
Seguir el procedimiento del Ejemplo 10, pero utilizar el compuesto del Ejemplo 33 como el producto de partida para obtener el compuesto del título.

MS (ESI) m/z 504 (M+H); RMN ^1H (DMSO- d_6) δ 0,91 (t, $J = 7,5$ Hz, 3H), 1,36 (m, 2H), 1,67 (m, 2H), 2,80 (m, 2H), 2,88 (m, 4H), 5,33 (s, 2H), 6,83-6,93 (m, 2H), 6,97 (s ancho, 1H), 7,23 (t, $J = 8,0$ Hz, 1H), 7,85 (d ancho, $J = 8,5$ Hz, 2H), 8,12 (d ancho, $J = 8,5$ Hz, 2H), 11,5-12,5 (m ancho, 1H).

REIVINDICACIONES

1. Un compuesto de fórmula I:

5



I

en la que

- 10 **ARILO** es fenilo o piridinilo, en el que dicho fenilo o piridinilo está opcionalmente sustituido con uno o más sustituyentes seleccionados del grupo que consiste en halógeno, alquiloC₁₋₆, alqueniloC₂₋₆, alcoxiC₁₋₆, perfluoroalquiloC₁₋₆; alquiltioC₁₋₆, hidroxil, hidroxialquiloC₁₋₆, aciloxiC₁₋₄, nitro, ciano, alquilsulfoniloC₁₋₆, amino, alquilaminoC₁₋₆ y alcoxiC₁₋₆carbonilo;
- 15 **W** es un enlace o (CH₂)_m, en el que m es un número entero de 1 a 4;
Z es -O(CH₂)_n-, -SO₂(CH₂)_n-, -(CH₂)_n-Y-(CH₂)_n-, -(CH₂)_n-CO-, -O(CH₂)_n-CO- o -(CH₂)_n-Y-(CH₂)_n-CO- en el que Y es NR₃, O o S y R₃ se seleccionan del grupo que consiste en H, alquiloC₁₋₆, cicloalquiloC₃₋₈, alquilC₁₋₆cicloalquiloC₃₋₈ y bencilo y n es independientemente un número entero de 1 a 5;
- 20 **X** es NR₃, O o S en el que R₃ es como se define más arriba;
R₁ es H, halógeno, alquiloC₁₋₆, alcoxiC₁₋₆, perfluoroalquiloC₁₋₆; hidroxialquiloC₁₋₆, nitro, ciano, y alquilC₁₋₆amino; y
R₂ es fenilo, piridinilo o tienilo sustituidos o no sustituidos en los que los sustituyentes se seleccionan del grupo que consiste en halógeno, alquiloC₁₋₆, alqueniloC₂₋₆, alcoxiC₁₋₄, perfluoroalquiloC₁₋₄, alquiltioC₁₋₆, hidroxil, hidroxialquiloC₁₋₆, aciloxiC₁₋₄, nitro, ciano, alquilC₁₋₆sulfonilo, amino, alquilC₁₋₆amino y alcoxiC₁₋₆carbonilo; o un estereoisómero, un tautómero o un solvato del mismo o una sal farmacéuticamente aceptable del mismo.
- 25

2. El compuesto según la reivindicación 1, en el que ARILO es fenilo
3. El compuesto según la reivindicación 1, en el que ARILO es fenilo; y
R₂ es fenilo.
- 5
4. El compuesto según la reivindicación 1, en el que ARILO es fenilo;
Z es -O(CH₂)_n-; y
R₂ es fenilo.
- 10
5. El compuesto según la reivindicación 1, en el que ARILO es fenilo;
Z es -O(CH₂)_n-;
X es O o S; y
R₂ es fenilo.
- 15
6. El compuesto según la reivindicación 1, en el que ARILO es fenilo;
Z es -O(CH₂)_n-;
X es O o S;
R₁ es alquiloC₁₋₆;
R₂ es fenilo y;
20 W es un enlace.
7. El compuesto según la reivindicación 6, en el que X es O.
8. El compuesto según la reivindicación 6, en el que X es S.
- 25
9. El compuesto según la reivindicación 1, en el que ARILO es fenilo;
Z es -(CH₂)_n-Y-(CH₂)_n-; y
R₂ es fenilo.
- 30
10. El compuesto según la reivindicación 1, en el que ARILO es fenilo;
Z es -(CH₂)_n-Y-(CH₂)_n-;
X es O o S; y

R₂ es fenilo.

11. El compuesto según la reivindicación 1, en el que ARILO es fenilo;

Z es $-(CH_2)_n-Y-(CH_2)_n-$;

X es O o S; y

5 R₁ es alquiloC₁₋₆;

R₂ es fenilo y;

W es un enlace.

12. El compuesto según la reivindicación 11, en el que X es S.

10

13. El compuesto según la reivindicación 11, en el que Y es O.

14. El compuesto según la reivindicación 1, en el que ARILO es fenilo;

Z es $-O(CH_2)_n-$;

15 X es O o S;

R₁ es alquiloC₁₋₆;

R₂ es fenilo y;

W es $(CH_2)_m$, en el que m es un número entero de 1 a 4.

20 15. El compuesto según la reivindicación 14, en el que X es S.

16. El compuesto según la reivindicación 1, que se selecciona del grupo que consiste en:

5- $\{4-[4\text{-metil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi}]\text{-fenil}\}$ -3H-[1,3,4]oxadiazol-2-

ona, 5- $\{4-(4\text{-metil-2-}m\text{-tolil-oxazol-5-ilmetoxi})\text{-fenil}\}$ -3H-[1,3,4]oxadiazol-2-ona, 5- $\{4-$

25 $[4\text{-metil-2-(4-trifluorometil-fenil)-tiazol-5-il}\}\text{-metoximetil}\}\text{-fenil}\}$ -3H-[1,3,4]oxadiazol-

2-ona, 5- $\{3-[4\text{-metil-2-(4-trifluorometil-fenil)-tiazol-5-il}\}\text{-metoximetil}\}\text{-fenil}\}$ -3H-

[1,3,4]oxadiazol-2-ona, 5- $\{4-[4\text{-butil-2-(4-trifluorometil-fenil)-tiazol-5-ilmetoxi}\}\text{-2-}$

cloro-fenil}\}-3H-[1,3,4]oxadiazol-2-ona, 5- $\{4-[4\text{-butil-2-(4-trifluorometil-fenil)-tiazol-5-}$

ilmetoximetil}\}\text{-2-fluoro-fenil}\}-3H-[1,3,4]oxadiazol-2-ona, 5- $\{4-[4\text{-butil-2-(4-trifluoro-}$

30 $\text{metil-fenil)-tiazol-5-ilmetoxi}\}\text{-bencil}\}\text{-3H-[1,3,4]oxadiazol-2-ona, y 5-(2-\{3-[4-butil-2-}$

$(4\text{-trifluorometil-fenil)-tiazol-5-ilmetoxi}\}\text{-fenil}\}\text{-etil}\}$ -3H-[1,3,4]oxadiazol-2-ona.

17. Una composición farmacéutica que comprende una cantidad eficaz de un compuesto según la reivindicación 1 y un vehículo farmacéuticamente aceptable.
- 5 18. Un método para tratar una enfermedad en un mamífero en el que la enfermedad es capaz de ser modulada por la actividad de unión del ligando del PPARdelta, que comprende administrar a dicho mamífero que tiene dicha enfermedad una cantidad terapéuticamente eficaz de un compuesto según la reivindicación 1.
- 10 19. El método según la reivindicación 11, en el que dicha enfermedad es una enfermedad desmielinizante seleccionada del grupo que consiste en esclerosis múltiple, enfermedad de Charcot-Marie-Tooth, enfermedad de Pelizaeus-Merzbacher, encefalomielitis, neuromielitis óptica, adrenoleucodistrofia, síndrome de Guillian-Barre y trastornos en los que las células gliales formadoras de mielina están dañadas que incluyen lesiones de la médula espinal, neuropatías y lesión nerviosa.
- 15 20. El método según la reivindicación 12, en el que la enfermedad desmielinizante es la esclerosis múltiple.
- 20 21. El método según la reivindicación 11 en el que dicha enfermedad se selecciona del grupo que consiste en obesidad, hipertrigliceridemia, hiperlipidemia, hipoalfalipoprotei-
nemia, hipercolesterolemia, dislipidemia, Síndrome X, diabetes mellitus de Tipo II y complicaciones de las mismas seleccionadas del grupo que consiste en neuropatía, nefropatía, retinopatía y cataratas, hiperinsulinemia, disminución de la tolerancia a la glu-
25 cososa, insulinoresistencia, aterosclerosis, hipertensión, enfermedad coronaria cardíaca, enfermedad vascular periférica o insuficiencia cardíaca congestiva.

RESUMEN

La presente invención está dirigida a 1,3,4-oxadiazolonas, compuestos de fórmula I y las sales, estereoisómeros, tautómeros, o solvatos farmacéuticamente aceptables de los mismos. Los Compuestos novedosos incluyen los de fórmula I, en la que los radicales son como se definen en la presente memoria.



I

Los compuestos de esta invención son moduladores del PPARdelta y por lo tanto útiles como agentes farmacéuticos, especialmente para el tratamiento de enfermedades desmielinizantes y trastornos del metabolismo de ácidos grasos y de utilización de la glucosa.

US20030122WO

1/11

PCT REQUEST

Original (for SUBMISSION)

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form PCT/RO/101 PCT Request	
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.169)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	US20030122WO
I	Title of invention	1,3,4-OXADIAZOL-2-ONES AS PPAR DELTA MODULATORS AND THEIR USE THEREOF
II	Applicant	
II-1	This person is	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	AVENTIS PHARMACEUTICALS INC.
II-5	Address	300 Somerset Corporate Boulevard Bridgewater, New Jersey 08807-2854 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	(908) 231-3800
II-9	Facsimile No.	(908) 231-2626
III-1	Applicant and/or inventor	
III-1-1	This person is	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	MCGARRY, Daniel, G.
III-1-5	Address	205 Carol Jean Way Branchburg, New Jersey 08876 United States of America
III-1-6	State of nationality	GB
III-1-7	State of residence	US

PCT REQUEST

Original (for SUBMISSION)

II-2	Applicant and/or inventor	
III-2-1	This person is	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	CHANDROSS, Karen
III-2-5	Address	13 Staudt Court Somerset, NJ 08873 United States of America
III-2-6	State of nationality	US
III-2-7	State of residence	US
II-3	Applicant and/or inventor	
III-3-1	This person is	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	MERRILL, Jean
III-3-5	Address	101 Alpine Lane Whippany, New Jersey 07981 United States of America
III-3-6	State of nationality	US
III-3-7	State of residence	US
II-4	Applicant and/or inventor	
III-4-1	This person is	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	GOERLITZER, Jochen
III-4-5	Address	Stegstrasse 60 D-60594 Frankfurt am Main Germany
III-4-6	State of nationality	DE
III-4-7	State of residence	DE
II-5	Applicant and/or inventor	
III-5-1	This person is	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	KEIL, Stefanie
III-5-5	Address	Am Kreishaus 12 65719 Hofheim Germany
III-5-6	State of nationality	DE
III-5-7	State of residence	DE

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Original (for SUBMISSION)

III-6	Applicant and/or inventor	
III-6-1	This person is	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	WENDLER, Wolfgang
III-6-5	Address	Haintchener Str. 12a 65618 Selters Germany
III-6-6	State of nationality	DE
III-6-7	State of residence	DE
III-7	Applicant and/or inventor	
III-7-1	This person is	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	BERNARDELLI, Patrick
III-7-5	Address	14 rue Auguste Rodin 78450 Villepreux France
III-7-6	State of nationality	FR
III-7-7	State of residence	FR
IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	STRUPCZEWSKI, Joseph
IV-1-2	Address	sanofi-aventis Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
IV-1-3	Telephone No.	(908) 231-2387
IV-1-4	Facsimile No.	(908) 231-2626
IV-1-5	e-mail	joseph.strupczewski@sanofi-aventis.com
IV-1-6	Agent's registration No.	50903
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	BARNEY, Charlotte, L. (35060); BENDER, Kelly (52610); BOLCSAK, James, W. (39912); COPPOLA, William, C. (41686); DAHLING, Gerald, V. (29632); DARKES, Paul, R. (33862); DOLAN, Peter, L. (46307); GERMAN, Joel, B. (48676); GUPTA, Balaram (40009); KIRK, Joseph, P.,

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Original (for SUBMISSION)

		Jr. (36844); KNIGHT, Julie, Anne (48867); KRUPEN, Karen, I. (34647); KURYS, Barbara, E. (34650); LIN, Jiang (51065); MOON, Carolyn, D. (33022); NELLIGAN, Mark, C. (36389); NEWMAN, Irving (22638); OEHLER, Ross, J. (33270); ORT, Ronald, G. (36969); PARKER, Raymond, S., III (34893); ROSSI, Joseph (47038)
V	DESIGNATIONS	
V-1	The filing of this request constitutes under Rule 4.2(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.	
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	01 April 2004 (01.04.2004)
VI-1-2	Number	60/558,419
VI-1-3	Country	US
VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)
VIII	Declarations	Number of declarations
VIII-1	Declaration as to the identity of the inventor	-
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	1
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	1
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-

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Original (for SUBMISSION)

VIII-3-1	Declaration: Entitlement to claim priority 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(II) and 51bis.1(a)(III)) Name	in relation to this international application AVENTIS PHARMACEUTICALS INC. is entitled to claim priority of earlier application No. 60/558,419 by virtue of the following:
VIII-3-1(i) v)		an assignment from MCGARRY, Daniel, G. to AVENTIS PHARMACEUTICALS INC., dated 17 May 2004 (17.05.2004)
VIII-3-1(i) v)		an assignment from CHANDROSS, Karen to AVENTIS PHARMACEUTICALS INC., dated 13 May 2004 (13.05.2004)
VIII-3-1(i) v)		an assignment from MERRILL, Jean to AVENTIS PHARMACEUTICALS INC., dated 16 May 2004 (16.05.2004)
VIII-3-1(i) v)		an assignment from GOERLITZER, Jochen to AVENTIS PHARMA DEUTSCHLAND GMBH, dated 13 May 2004 (13.05.2004)
VIII-3-1(i) v)		an assignment from KEIL, Stefanie to AVENTIS PHARMA DEUTSCHLAND GMBH, dated 14 May 2004 (14.05.2004)
VIII-3-1(i) v)		an assignment from WENDLER, Wolfgang to AVENTIS PHARMA DEUTSCHLAND GMBH, dated 17 May 2004 (17.05.2004)
VIII-3-1(i) v)		an assignment from AVENTIS PHARMA DEUTSCHLAND GMBH to AVENTIS PHARMACEUTICALS INC., dated 14 June 2004 (14.06.2004)
VIII-3-1(i) x)	This declaration is made for the purposes of:	all designations

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VII-4-1	Declaration: Inventorship (only for the purposes of the designation of the United States of America) 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). 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 Applications", 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.
VIII-4-1-1	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 application. 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.
VII-4-1-1-1	Name (LAST, First)	MCGARRY, Daniel, G.
VII-4-1-1-2	Residence: (city and either US State, if applicable, or country)	Branchburg, New Jersey
VII-4-1-1-3	Mailing address:	205 Carol Jean Way Branchburg, NJ 08876 United States of America
VII-4-1-1-4	Citizenship:	GB
VII-4-1-1-5	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)	
VII-4-1-1-6	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)	 8/4/05

PCT REQUEST

Original (for SUBMISSION)

VIII-4-1-2-1	Name (LAST, First)	CHANDROSS, Karen
VIII-4-1-2-2	Residence: (city and either US State, if applicable, or country)	Somerset,
VIII-4-1-2-3	Mailing address:	13 Staudt Court Somerset, NJ 08873 United States of America
VIII-4-1-2-4	Citizenship:	US
VIII-4-1-2-5	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)	
VIII-4-1-2-6	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)	Karen Chandross 5/4/05
VIII-4-1-3-1	Name (LAST, First)	MERRILL, Jean
VIII-4-1-3-2	Residence: (city and either US State, if applicable, or country)	Whippany, New Jersey
VIII-4-1-3-3	Mailing address:	101 Alpine Lane Whippany, NJ 07981 United States of America
VIII-4-1-3-4	Citizenship:	US
VIII-4-1-3-5	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)	
VIII-4-1-3-6	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)	Jean Merrill 5-6-05

PCT REQUEST

Original (for SUBMISSION)

VII-4-1-4-1	Name (LAST, First)	GOERLITZER, Jochen
VII-4-1-4-2	Residence: (city and either US State, if applicable, or country)	Frankfurt am Main, Germany
VII-4-1-4-3	Mailing address:	Stegstrasse 60 D-60594 Frankfurt am Main Germany
VII-4-1-4-4	Citizenship:	DE
VII-4-1-4-5	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)	<i>Jochen Goerlitz</i>
VII-4-1-4-8	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)	11/05/2005
VIII-4-1-5-1	Name (LAST, First)	KEIL, Stefanie
VIII-4-1-5-2	Residence: (city and either US State, if applicable, or country)	Hofheim, Germany
VIII-4-1-5-3	Mailing address:	Am Kreishaus 12 65719 Hofheim Germany
VIII-4-1-5-4	Citizenship:	DE
VIII-4-1-5-5	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)	<i>Stefanie Keil</i>
VIII-4-1-5-8	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)	18/05/2005

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PCT REQUEST

Original (for SUBMISSION)

VIII-4-1- 8-1	Name (LAST, First)	WENDLER, Wolfgang
VIII-4-1- 8-2	Residence: (city and either US State, if applicable, or country)	Selters, Germany
VIII-4-1- 8-3	Mailing address:	Haintchener Str. 12a 65618 Selters Germany
VIII-4-1- 8-4	Citizenship:	DE
VIII-4-1- 8-5	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)	<i>Wolfgang Wendler</i>
VIII-4-1- 8-8	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)	<i>May 18, 2005</i>
VIII-4-1- 7-1	Name (LAST, First)	BERNARDELLI, Patrick
VIII-4-1- 7-2	Residence: (city and either US State, if applicable, or country)	Villepreux, France
VIII-4-1- 7-3	Mailing address:	14 rue Auguste Rodin 78450 Villepreux France
VIII-4-1- 7-4	Citizenship:	FR
VIII-4-1- 7-5	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)	
VIII-4-1- 7-8	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)	

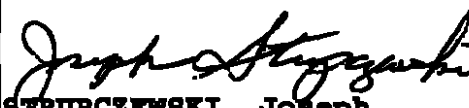
PCT REQUEST

Original (for SUBMISSION)

VIII-4-1-6-1	Name (LAST, First)	WENDLER, Wolfgang
VIII-4-1-6-2	Residence: (city and either US State, if applicable, or country)	Selters, Germany
VIII-4-1-6-3	Mailing address:	Haintchener Str. 12a 65618 Selters Germany
VIII-4-1-6-4	Citizenship:	DE
VIII-4-1-6-5	Inventor's Signature: (If not contained in the request, or if declaration is corrected or added under Rule 28ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-6-8	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 28ter after the filing of the international application)	
VIII-4-1-7-1	Name (LAST, First)	BERNARDELLI, Patrick
VIII-4-1-7-2	Residence: (city and either US State, if applicable, or country)	Villepreux, France
VIII-4-1-7-3	Mailing address:	14 rue Auguste Rodin 78450 Villepreux France
VIII-4-1-7-4	Citizenship:	FR
VIII-4-1-7-5	Inventor's Signature: (If not contained in the request, or if declaration is corrected or added under Rule 28ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-7-8	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 28ter after the filing of the international application)	May 7, 2005

PCT REQUEST

Original (for SUBMISSION)

IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	11	/
IX-2	Description	62	-
IX-3	Claims	4	-
IX-4	Abstract	1	/
IX-5	Drawings	0	-
IX-7	TOTAL	78	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	/	-
IX-9	Original separate power of attorney	/	-
IX-17	PCT-SAFE physical media	-	/
IX-18	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative	 STRUPCZEWSKI, Joseph	
X-1-1	Name (LAST, First)		
X-1-2	Name of signatory		
X-1-3	Capacity		

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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EL964825455US

US20030122WO

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PCT POWER OF ATTORNEY

Duplicate of Original

0-1	PCT Power of Attorney (for an international application filed under the Patent Cooperation Treaty) (PCT Rule 92.4)	
0-1-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.169)

PCT POWER OF ATTORNEY

Duplicate of Original

1	The undersigned applicant(s)	AVENTIS PHARMACEUTICALS INC.; MCGARRY, Daniel, G.; CHANDROSS, Karen; MERRILL, Jean; GOERLITZER, Jochen; KEIL, Stefanie; WENDLER, Wolfgang; BERNARDELLI, Patrick
1-1-1	hereby appoints (appoint) the following person	STRUPCZEWSKI, Joseph sanofi-aventis Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
1-1-2	hereby appoints (appoint) the following person	BARNET, Charlotte, L. sanofi-aventis Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
1-1-3	hereby appoints (appoint) the following person	BENDER, Kelly sanofi-aventis Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
1-1-4	hereby appoints (appoint) the following person	BOLCSAK, James, W. sanofi-aventis Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
1-1-5	hereby appoints (appoint) the following person	COPPOLA, William, C. sanofi-aventis Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
1-1-6	hereby appoints (appoint) the following person	DAHLING, Gerald, V. sanofi-aventis Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
1-1-7	hereby appoints (appoint) the following person	DARKES, Paul, R. sanofi-aventis Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
1-1-8	hereby appoints (appoint) the following person	DOLAN, Peter, L. sanofi-aventis Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
1-1-9	hereby appoints (appoint) the following person	GERMAN, Joel, B. sanofi-aventis

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PCT POWER OF ATTORNEY

Duplicate of Original

		Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
1-1-10	hereby appoints (appoint) the following person	GUPTA, Balaran sanofi-aventis Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
1-1-11	hereby appoints (appoint) the following person	KIRK, Joseph, P., Jr. sanofi-aventis Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
1-1-12	hereby appoints (appoint) the following person	KNIGHT, Julie, Anne sanofi-aventis Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
1-1-13	hereby appoints (appoint) the following person	KRUPEN, Karen, I. sanofi-aventis Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
1-1-14	hereby appoints (appoint) the following person	KURYS, Barbara, E. sanofi-aventis Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
1-1-15	hereby appoints (appoint) the following person	LIN, Jiang sanofi-aventis Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
1-1-16	hereby appoints (appoint) the following person	MOON, Carolyn, D. sanofi-aventis Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
1-1-17	hereby appoints (appoint) the following person	NELLIGAN, Mark, C. sanofi-aventis Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
1-1-18	hereby appoints (appoint) the following person	NEWMAN, Irving sanofi-aventis Route 202-206 P. O. Box 6800

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PCT POWER OF ATTORNEY

Duplicate of Original

		Bridgewater, NJ 08807-0800 United States of America
1-1-18	hereby appoints (appoint) the following person	OEHLER, Ross, J. sanofi-aventis Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
1-1-20	hereby appoints (appoint) the following person	ORT, Ronald, G. sanofi-aventis Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
1-1-21	hereby appoints (appoint) the following person	PARKER, Raymond, S., III sanofi-aventis Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
1-1-22	hereby appoints (appoint) the following person	ROSSI, Joseph sanofi-aventis Route 202-206 P. O. Box 6800 Bridgewater, NJ 08807-0800 United States of America
1-2	as	agent
1-3	to represent the undersigned before	all the competent International Authorities
1-4	in connection with the international application identified below:	
1-4-1	Title of invention	1,3,4-OXADIAZOL-2-ONES AS PPAR DELTA MODULATORS AND THEIR USE THEREOF
1-4-2	Applicant's or agent's file reference	US20030122WO
1-4-3	International application number (if already available)	
1-4-4	Filed with the following Office as receiving Office	United States Patent and Trademark Office (USPTO) (RO/US)
1-5	and to make or receive payments on behalf of the undersigned	

2-1	Signature of applicant, agent or common representative	
2-1-1	Name	AVANTIS PHARMACEUTICALS INC.
2-1-2	Name of signatory	Ross J. Oehler
2-1-3	Capacity	Vice President
2-2	Signature of applicant, agent or common representative	
2-2-1	Name (LAST, First)	MCGARRY, Daniel, G.
2-2-2	Name of signatory	
2-2-3	Capacity	

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PCT POWER OF ATTORNEY

Duplicate of Original

2-3	Signature of applicant, agent or common representative	
2-3-1	Name (LAST, First)	CHANDROSS, Karen
2-3-2	Name of signatory	
2-3-3	Capacity	
2-4	Signature of applicant, agent or common representative	
2-4-1	Name (LAST, First)	MERRILL, Jean
2-4-2	Name of signatory	
2-4-3	Capacity	
2-5	Signature of applicant, agent or common representative	
2-5-1	Name (LAST, First)	GOERLITZER, Jochen
2-5-2	Name of signatory	
2-5-3	Capacity	
2-6	Signature of applicant, agent or common representative	
2-6-1	Name (LAST, First)	KEIL, Stefanie
2-6-2	Name of signatory	
2-6-3	Capacity	
2-7	Signature of applicant, agent or common representative	
2-7-1	Name (LAST, First)	WENDLER, Wolfgang
2-7-2	Name of signatory	
2-7-3	Capacity	
2-8	Signature of applicant, agent or common representative	
2-8-1	Name (LAST, First)	BERNARDELLI, Patrick
2-8-2	Name of signatory	
2-8-3	Capacity	
3	Date	30 March 2005 (30.03.2005)

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PCT POWER OF ATTORNEY

Duplicate of Original

2-3	Signature of applicant, agent or common representative	
2-3-1	Name (LAST, First)	CHANDROSS, Karen <i>Karen Chandross</i>
2-3-2	Name of signatory	
2-3-3	Capacity	
2-4	Signature of applicant, agent or common representative	
2-4-1	Name (LAST, First)	MERRILL, Jean <i>Jean Merrill</i>
2-4-2	Name of signatory	
2-4-3	Capacity	
2-5	Signature of applicant, agent or common representative	
2-5-1	Name (LAST, First)	GOERLITZER, Jochen
2-5-2	Name of signatory	
2-5-3	Capacity	
2-6	Signature of applicant, agent or common representative	
2-6-1	Name (LAST, First)	KEIL, Stefanie
2-6-2	Name of signatory	
2-6-3	Capacity	
2-7	Signature of applicant, agent or common representative	
2-7-1	Name (LAST, First)	WENDLER, Wolfgang
2-7-2	Name of signatory	
2-7-3	Capacity	
2-8	Signature of applicant, agent or common representative	
2-8-1	Name (LAST, First)	BERNARDELLI, Patrick
2-8-2	Name of signatory	
2-8-3	Capacity	
3	Date	30 March 2005 (30.03.2005)

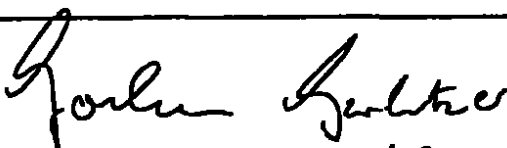
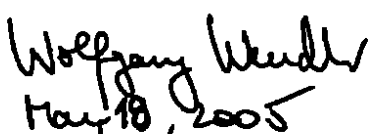
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US20030122WD

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PCT POWER OF ATTORNEY

Duplicate of Original

2-3	Signature of applicant, agent or common representative	
2-3-1	Name (LAST, First)	CHANDROSS, Karen
2-3-2	Name of signatory	
2-3-3	Capacity	
2-4	Signature of applicant, agent or common representative	
2-4-1	Name (LAST, First)	MERRILL, Jean
2-4-2	Name of signatory	
2-4-3	Capacity	
2-5	Signature of applicant, agent or common representative	
2-5-1	Name (LAST, First)	GOERLITZER, Jochen 18/05/2005
2-5-2	Name of signatory	
2-5-3	Capacity	
2-6	Signature of applicant, agent or common representative	
2-6-1	Name (LAST, First)	KEIL, Stefanie 18/05/2005
2-6-2	Name of signatory	
2-6-3	Capacity	
2-7	Signature of applicant, agent or common representative	
2-7-1	Name (LAST, First)	WENDLER, Wolfgang 
2-7-2	Name of signatory	
2-7-3	Capacity	May 18, 2005
2-8	Signature of applicant, agent or common representative	
2-8-1	Name (LAST, First)	BERNARDELLI, Patrick
2-8-2	Name of signatory	
2-8-3	Capacity	
3	Date	30 March 2005 (30.03.2005)

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

From the INTERNATIONAL BUREAU

To:

STRUPCZEWSKI, Joseph
sanofi-aventis
Route 202-206
P. O. Box 6800
Bridgewater, NJ 08807-0800
ETATS-UNIS D'AMERIQUE

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year) 09 September 2005 (09.09.2005)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference US20030122WO	
International application No. PCT/US2005/010854	International filing date (day/month/year) 30 March 2005 (30.03.2005)
International publication date (day/month/year)	Priority date (day/month/year) 01 April 2004 (01.04.2004)
Applicant AVENTIS PHARMACEUTICALS INC. et al	

- By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- (If applicable) An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date

Priority application No.

Country or regional Office
or PCT receiving Office

Date of receipt
of priority document

01 April 2004 (01.04.2004)

60/558,419

US

12 August 2005 (12.08.2005)

ACTION DUE

DUE DATE

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Françoise HENNEQUIN (Fax 338 7010)

Facsimile No. (41-22) 338.70.10

Telephone No. +41 22 338 9935

Facsimile No. +41 22 338 82 70

Form PCT/IB/304 (January 2004)

CKR0LK6J

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

STRUPCZEWSKI, Joseph
sanofi-aventis
Route 202-206
P. O. Box 6800
Bridgewater, NJ 08807-0800
United States of America

Date of mailing (day/month/year)

01 September 2005 (01.09.2005)

Applicant's or agent's file reference

US20030122WO

International application No.

PCT/US2005/010854

International filing date (day/month/year)

30 March 2005 (30.03.2005)

IMPORTANT NOTIFICATION

1. The following indications appeared on record concerning:

☐

the applicant

☐

the inventor

☒

the agent

☐

the common representative

Name and Address

ROSSI, Joseph
sanofi-aventis
Route 202-206
P. O. Box 6800
Bridgewater, NJ 08807-0800
United States of America
(Additional agent)

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒

the person

☐

the name

☐

the address

☐

the nationality

☐

the residence

Name and Address

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

Revocation and renunciation of appointment.

4. A copy of this notification has been sent to:

☒

the receiving Office

☒

the International Searching Authority

☐

the International Preliminary Examining Authority

☐

the designated Offices concerned

☐

the elected Offices concerned

☐

other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.70.10

Authorized officer

MIKI KOBAYASHI (Fax 338 7010)

Telephone No. (41-22) 338 9401

INTERNATIONAL 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/US2005/010854

International filing date (day/month/year)
30.03.2005

Priority date (day/month/year)
01.04.2004

International Patent Classification (IPC) or both national classification and IPC
C07D417/12, C07D413/12, A61K31/4245, A61P3/10, A61P3/08

Applicant
AVENTIS PHARMACEUTICALS INC.

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"). However, 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 86.1bis(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 three 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.

Prepare Reply To Written Opinion - 1/1/06

ACTION DUE Reply Due - 2/1/06

DUE DATE 2/1/06

Name and mailing address of the ISA:



European Patent Office
D-80288 Munich
Tel. +49 89 2399-0 Tx: 523658 epmu d
Fax: +49 89 2399-4465

Authorized Officer

Herz, C

Yes 10/4/05
J. Strupczewski

Telephone No. +49 89 2399-8275

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/010854

124
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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, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. 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:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ 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.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/010854

125
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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. 18-21

because:

- ☒ the said international application, or the said claims Nos. 18-21 relate to the following subject matter which does not require an International preliminary examination (*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.
- ☐ no International search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
- the written form ☐ has not been furnished
☐ does not comply with the standard
- the computer readable form ☐ has not been furnished
☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No. **120**
128
PCT/US2005/010854

**Box No. V Reasoned statement under Rule 43b1.1(a)(I) with regard to novelty, inventive step or
Industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-17
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-17
Industrial applicability (IA)	Yes: Claims	1-17
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

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

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

125
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International application No.

PCT/US2005/010854

1. Claims 18 to 21 are directed to a therapeutical method performed on humans. Under the terms of Rule 67.1 (iv) PCT, the International Preliminary Examination Authority is not required to carry out an examination on such claims.

2. Due to the invariable presence of an 1,3,4-oxadiazol-2-one moiety the compounds claimed are considered to be novel vis-à-vis the state of the art as represented by the documents cited in the International Search Report (ISER).

With regard to the presence of inventive step reference is made to the documents classified "Y" in the ISER wherein similar compounds possessing PPAR δ modulating activity have been disclosed. Substituents therein are the same as or similar to those given in the present application.

Taking into account these facts the man skilled in the art would have to expect the PPAR δ modulating activity without affecting their fundamental capabilities when modifying the basic moiety and/or the substituents of the groups of compounds disclosed in the state of the art. Thus representing only predictable effects the compounds claimed are considered to be obvious.

Consequently, at present, Claims 1 to 17 are lacking inventive step under Article 33 (3) PCT.

Accordingly it is to be demonstrated wherein the inventive step lies in the compounds claimed, e.g. by showing a significant improvement in the property relevant to the solution of the stated problem. If it is chosen to give evidence using comparative tests, these must be carried out in respect of the closest state of the art.

3. Back references of claims 19 to 21 are incorrect since the claims referenced to are not method claims.

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference US20030122WO	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2005/010854	International filing date (day/month/year) 30/03/2005	(Earliest) Priority Date (day/month/year) 01/04/2004
Applicant AVENTIS PHARMACEUTICALS INC.		

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

This International Search Report consists of a total of 4 sheets.

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

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☐ 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 II).

3. ☐ Unity of invention is lacking (see Box 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:

1,3,4-OXADIAZOL-2-ONES AS PPAR DELTA MODULATORS

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
PC., JS2005/010854109
131

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D417/12 C07D413/12 A61K31/4245 A61P3/10 A61P3/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

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

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

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	S. S. KULKARNI ET AL.: "Three-Dimensional Quantitative Structure Activity Relationship (3-D-QSAR) of Antihyperglycemic Agents" BIOORG. MED. CHEM., vol. 7, 1999, pages 1475-1485, XP002345584 figure 1	1-21
Y	WO 00/78313 A (MERCK & CO., INC.) 28 December 2000 (2000-12-28) claims 1-30	1-21
A	WO 01/00603 A (GLAXO GROUP LTD.) 4 January 2001 (2001-01-04) claims 1-50	1-21
	-/-	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

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

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

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

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

A document member of the same patent family

Date of the actual completion of the international search

19 September 2005

Date of mailing of the international search report

29/09/2005

Name and mailing address of the ISA

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

Authorized officer

Herz, C

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2005/010854

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/17994 A (GLAXO GROUP LTD.) 15 March 2001 (2001-03-15) claims 1-20 -----	1-21
A	B. R. HENKE ET AL.: "N-(2-Benzoylphenyl)-L-tyrosine PPAR.gamma. Agonists. 1. Discovery of a Novel Series of Potent Antihyperglycemic and Antihyperlipidemic Agents" J. MED. CHEM., vol. 41, no. 25, 11 November 1998 (1998-11-11), pages 5020-5036, XP000864731 table 3 -----	1-21

INTERNATIONAL SEARCH REPORT

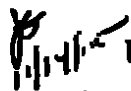
Information on patent family members

International Application No

PCT, JS2005/010854

431
133

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0078313	A	28-12-2000	AU 770870 B2	04-03-2004
			AU 5746800 A	09-01-2001
			CA 2377246 A1	28-12-2000
			EP 1194147 A1	10-04-2002
			JP 2003502370 T	21-01-2003
WO 0100603	A	04-01-2001	AT 297384 T	15-06-2005
			AU 765347 B2	18-09-2003
			AU 5817100 A	31-01-2001
			BR 0011891 A	05-03-2002
			CA 2377126 A1	04-01-2001
			CN 1358179 A	10-07-2002
			CZ 20014664 A3	13-03-2002
			DE 60020701 D1	14-07-2005
			EP 1189895 A1	27-03-2002
			HU 0201858 A2	28-09-2002
			JP 3490704 B2	26-01-2004
			JP 2003503399 T	28-01-2003
			JP 2003313141 A	06-11-2003
			MX PA01013244 A	02-07-2002
			NO 20016078 A	13-12-2001
			NZ 515676 A	28-05-2004
			PL 353135 A1	20-10-2003
			TR 200103612 T2	21-05-2002
WO 0117994	A	15-03-2001	US 6710063 B1	23-03-2004
			ZA 200109804 A	28-02-2003
			AT 260912 T	15-03-2004
			AU 7115300 A	10-04-2001
			DE 60008763 D1	08-04-2004
			DE 60008763 T2	10-02-2005
			EP 1210345 A1	05-06-2002
			ES 2215719 T3	16-10-2004
			JP 2003508529 T	04-03-2003



From the INTERNATIONAL BUREAU

PCT

FIRST NOTICE INFORMING THE APPLICANT OF
THE COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES WHICH
DO NOT APPLY THE 30 MONTH TIME LIMIT
UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

STRUPCZEWSKI, Joseph
sanofi-aventis
Route 202-206
P. O. Box 6800
Bridgewater, NJ 08807-0800
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 03 November 2005 (03.11.2005)		IMPORTANT NOTICE
Applicant's or agent's file reference US20030122WO		
International application No. PCT/US2005/010854	International filing date (day/month/year) 30 March 2005 (30.03.2005)	Priority date (day/month/year) 01 April 2004 (01.04.2004)
Applicant AVENTIS PHARMACEUTICALS INC. et al		

1. **ATTENTION:** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), does apply, please see Form PCT/IB/308(Second and Supplementary Notice) (to be issued promptly after the expiration of 28 months from the priority date).
2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, does not apply, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below:
20 October 2005 (20.10.2005)

CH

In accordance with Rule 47.1(c-bis)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, does not apply, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1:

LU, SE, TZ, UG, ZM

In accordance with Rule 47.1(c-bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

TIME LIMITS for entry into the national phase

For the designated Office(s) listed above, and unless a demand for international preliminary examination has been filed before the expiration of 19 months from the priority date (see Article 39(1)), the applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 20 MONTHS from the priority date.

In practice, time limits other than the 20-month time limit will continue to apply, for various periods of time, in respect of certain of the designated Offices listed above. For regular updates on the applicable time limits (20 or 21 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

It is the applicant's sole responsibility to monitor all these time limits.

NO ACTION DUE	file
FILE DATE	
FILED BY	Geo 11/10/05
	J.S.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Masashi Honda
Facsimile No.+41 22 740 14 35	Facsimile No.+41 22 338 70 10

From the INTERNATIONAL BUREAU

RECEIVED

AUG 09 2006

PATENT DEPT

PCT

SECOND AND SUPPLEMENTARY NOTICE
INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES
WHICH APPLY THE 30 MONTH TIME
LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

STRUPGZEWSKI, Joseph
sanofi-aventis
Route 202-206
P. O. Box 6800
Bridgewater, NJ 08807-0800
ETATS-UNIS D'AMERIQUE

I.H.
↓
Craig Bell

COMPUTER ENTERED

9/10 8/10/06

IMPORTANT NOTICE

Date of mailing (day/month/year)

03 August 2006 (03.08.2006)

Applicant's or agent's file reference

US20030122WO

International application No.

PCT/US2005/010854

International filing date (day/month/year)

30 March 2005 (30.03.2005)

Priority date (day/month/year)

01 April 2004 (01.04.2004)

Applicant

AVENTIS PHARMACEUTICALS INC. et al

1. ATTENTION: For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), does not apply, please see Form PCT/IB/308(First Notice) issued previously.
2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, does apply, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below:
20 October 2005 (20.10.2005)

AU, AZ, BY, CN, CO, DZ, EP, HU, KG, KP, KR, MD, MK, MZ, NA, PG, RU, SY, TM, US

In accordance with Rule 47.1(c-bis)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, does apply, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1:

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BW, BZ, CA, CR, CU, CZ, DE, DK, DM, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, JP, KE, KZ, LC, LK, LR, LS, LT, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PH, PL, PT, RO, SC, SD, SG, SK, SL, SM, TJ, TN, TR, TT, UA, UZ, VC, VN, YU, ZA, ZW

In accordance with Rule 47.1(c-bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. TIME LIMITS for entry into the national phase

For the designated or elected Office(s) listed above, the applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain of the designated or elected Office(s) listed above. For regular updates on the applicable time limits (30 or 31 months, or other time limit), Office by Office, refer to the PCT Gazette, the PCT Newsletter and the PCT Applicant's Guide, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 82 70

Authorized officer

Masashi Honda

e-mail: pt08@wipo.int



Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 08-088507- -00000-0000
Pag: 2006-08-22 12:23:36 Dep. 3020 NUECREACIONES
Tra. 11 PATENTEIYI
Ene: 376 FASENACIONAL
Act 411 PRESENTACION Folios: 133

136

Delegatura de Propiedad Industrial División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

PATENTE DE INVENCION ()	MODELO DE UTILIDAD ()	USUARIO ()	RADICADOR ()
-Indicación de que se solicita la concesión de una patente.		()	()
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.		()	()
-Descripción de la invención.		()	()
-Dibujos de ser estos pertinentes.		()	()
-Comprobante de Pago de las tasas establecidas.		()	()
COMPLETA ()	INCOMPLETA ()	()	()

DISEÑO INDUSTRIAL ()

-Indicación de que se solicita el registro de Diseño Industrial.	()	()
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
-Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
-Comprobante de Pago de las tasas establecidas.	()	()
COMPLETA ()	INCOMPLETA ()	()

ESQUEMA DE TRAZADO ()

-Indicación de que se solicita el registro de Diseño Industrial.	()	()
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
-Representación gráfica del Esquema Trazado.	()	()
-Comprobante de Pago de las tasas establecidas.	()	()
COMPLETA ()	INCOMPLETA ()	()

Firma Responsable: _____

Fecha: _____

13^x

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 138

2020
Bogotá D.C.,

Doctor(a)
PATIÑO LEYVA LUIS
Apoderado(a) y/o Representante de
AVENTIS PHARMACEUTICALS INC.

REFERENCIA	Radicación No.	06 98507
	Solicitud internacional	PCT/US2005/010854
	Fecha inicio fase nacional	01/11/2006
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No.	1925
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase

Dado en Bogotá DC,

28 NOV. 2006

ALIX CARMENZA OSSPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

salvarado